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RETROVIRAL PROTEASE INHIBITING COMPOUNDS

This is a continuation-in-part of U.S. patent application Serial No. 777,626, filed October 23, 1991, which is a continuation-in-part of U.S. patent application Serial No. 746,020, filed August 15, 1991, which is a continuation-in-part of U.S. patent application Serial No. 616,170, filed November 20, 1990, which is a continuation-in-part of U.S. patent application Serial No. 518,730, filed May 9, 1990, which is a continuation-in-part of U.S. patent application Serial No. 456,124, filed December 22, 1989, which is a continuation-in-part of U.S. patent application Serial No. 405,604, filed September 8, 1989, which is a continuation-in-part of U.S. patent application Serial No. 355,945, filed May 23, 1989.

Technical Field

This invention was made with Government support under contract number AI27220 awarded by the National Institute of Allergy and Infectious Diseases. The Government has certain rights in this invention.

The present invention relates to novel compounds and a composition and method for inhibiting retroviral proteases and in particular for inhibiting human immunodeficiency virus (HIV) protease, a composition and method for treating a

retroviral infection and in particular an HIV infection, processes for making such compounds and synthetic intermediates employed in these processes.

Background Art

Retroviruses are those viruses which utilize a ribonucleic acid (RNA) intermediate and a RNA-dependent deoxyribonucleic acid (DNA) polymerase, reverse transcriptase, during their life cycle. Retroviruses include, but are not limited to, the RNA viruses of the Retroviridae family, and also the DNA viruses of the Hepadnavirus and Caulimovirus families. Retroviruses cause a variety of disease states in man, animals and plants. Some of the more important retroviruses from a pathological standpoint include human immunodeficiency viruses (HIV-1 and HIV-2), which cause acquired immune deficiency syndrome (AIDS) in man, hepatitis B virus, which causes hepatitis and hepatic carcinomas in man, human T-cell lymphotrophic viruses I, II, IV and V, which cause human acute cell leukemia, and bovine and feline leukemia viruses which cause leukemia in domestic animals.

Proteases are enzymes which cleave proteins at specific peptide bonds. Many biological functions are controlled or mediated by proteases and their complementary protease inhibitors. For example, the protease renin cleaves the peptide angiotensinogen to produce the peptide angiotensin I. Angiotensin I is further cleaved by the protease angiotensin converting enzyme (ACE) to form the hypotensive peptide angiotensin II. Inhibitors of renin and ACE are known to reduce high blood pressure in vivo. An inhibitor of a retroviral protease will provide a therapeutic agent for diseases caused by the retrovirus.

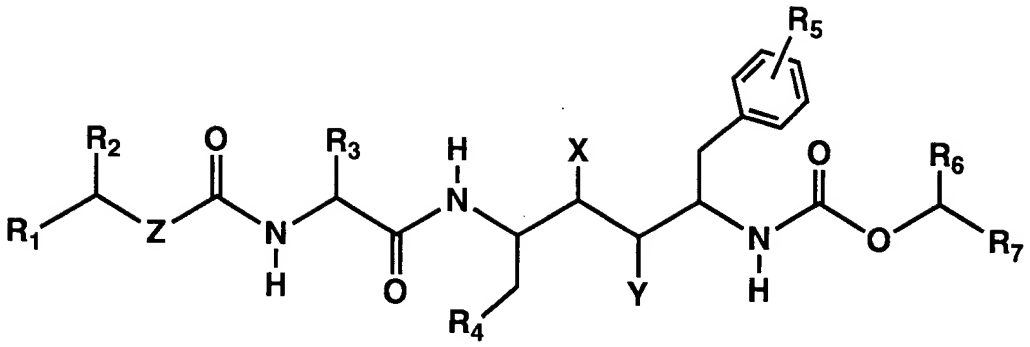
The genomes of retroviruses encode a protease that is responsible for the proteolytic processing of one or more polyprotein precursors such as the pol and gag gene products. See Wellink, Arch. Virol. 98 1 (1988). Retroviral proteases most commonly process the gag precursor into core proteins, and also process the pol precursor into reverse transciptase and retroviral protease. In addition, retroviral proteases are sequence specific. See Pearl, Nature 328 482 (1987).

The correct processing of the precursor polyproteins by the retroviral protease is necessary for the assembly of infectious virions. It has been shown that in vitro mutagenesis that produces protease-defective virus leads to the production of immature core forms which lack infectivity. See Crawford, J. Virol. 53 899 (1985); Katoh, et al., Virology 145 280 (1985). Therefore, retroviral protease inhibition provides an attractive target for antiviral therapy. See Mitsuya, Nature 325 775 (1987).

Current treatments for viral diseases usually involve administration of compounds that inhibit viral DNA synthesis. Current treatments for AIDS (Dagani, Chem. Eng. News, November 23, 1987 pp. 41-49) involve administration of compounds such as 2',3'-dideoxycytidine, 2',3'-dideoxyinosine, trisodium phosphonoformate, ammonium 21-tungsto-9-antimoniate, 1-beta-D-ribofuranosyl-1,2,4-triazole-3-carboxamide, 3'-azido-3'-deoxythymidine, and adriamycin that inhibit viral DNA synthesis; compounds such as AL-721 and polymannoacetate which may prevent HIV from penetrating the host cell; and compounds which treat the opportunistic infections caused by the immunosuppression resulting from HIV infection. None of the current AIDS treatments have proven to be totally effective in treating and/or reversing the disease. In addition, many of the compounds currently used to treat AIDS cause adverse side effects including low platelet count, renal toxicity and bone marrow cytopenia.

Disclosure of the Invention

In accordance with the present invention, there are retroviral protease inhibiting compounds of the formula **A**:



A

wherein R_1 is monosubstituted thiazolyl, monosubstituted oxazolyl, monosubstituted isoxazolyl or monosubstituted isothiazolyl wherein the substituent is selected from (i) loweralkyl, (ii) loweralkenyl, (iii) cycloalkyl, (iv) cycloalkylalkyl, (v) cycloalkenyl, (vi)cycloalkenylalkyl, (vii) heterocyclic wherein the heterocyclic is selected from aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyridazinyl and pyrazinyl and wherein the heterocyclic is unsubstituted or substituted with a substituent selected from halo, loweralkyl, hydroxy, alkoxy and thioalkoxy, (viii) (heterocyclic)alkyl wherein heterocyclic is defined as above, (ix) alkoxyalkyl,
(x) thioalkoxyalkyl, (xi) alkylamino, (xii) dialkylamino, (xiii) phenyl wherein the phenyl ring is unsubstituted or substituted with a substituent selected from halo, loweralkyl, hydroxy, alkoxy and thioalkoxy, (xiv) phenylalkyl wherein the phenyl ring is unsubstituted or substituted as defined above,
(xv) dialkylaminoalkyl, (xvi) alkoxy and (xvii) thioalkoxy;

R_2 is hydrogen or loweralkyl;

R_3 is loweralkyl;

R_4 is phenyl, thiazolyl or oxazolyl wherein the phenyl, thiazolyl or oxazolyl ring is unsubstituted or substituted with a substituent selected from

(i) halo, (ii) loweralkyl, (iii) hydroxy, (iv) alkoxy and (v) thioalkoxy;

R_5 is hydrogen, halo, loweralkyl, hydroxy, alkoxy or thioalkoxy;

R_6 is hydrogen or loweralkyl;

R_7 is thiazolyl, oxazolyl, isoxazolyl or isothiazolyl wherein the thiazolyl, oxazolyl, isoxazolyl or isothiazolyl ring is unsubstituted or substituted with loweralkyl;

X is hydrogen and Y is -OH or X is -OH and Y is hydrogen, with the proviso that X is hydrogen and Y is -OH when Z is -N(R_8)- and R_7 is unsubstituted and with the proviso that X is hydrogen and Y is -OH when R_3 is methyl and R_7 is unsubstituted;

Z is -O-, -S-, -CH_2- or -N(R_8)- wherein R_8 is loweralkyl or cycloalkyl; or a pharmaceutically acceptable salt, ester or prodrug thereof.

Preferred compounds of the formula **A** are those wherein R_1 is monosubstituted thiazolyl or monosubstituted oxazolyl; R_2 is hydrogen; R_4 is phenyl or thiazolyl; R_5 is hydrogen; R_6 is hydrogen and R_7 is thiazolyl, oxazolyl, isothiazolyl or isoxazolyl.

More preferred compounds of the formula **A** are those wherein R_1 is 2-monosubstituted-4-thiazolyl or 2-monosubstituted-4-oxazolyl; R_2 is hydrogen; R_4 is phenyl; R_5 is hydrogen; R_6 is hydrogen and R_7 is 5-thiazolyl, 5-oxazolyl, 5-isothiazolyl or 5-isoxazolyl.

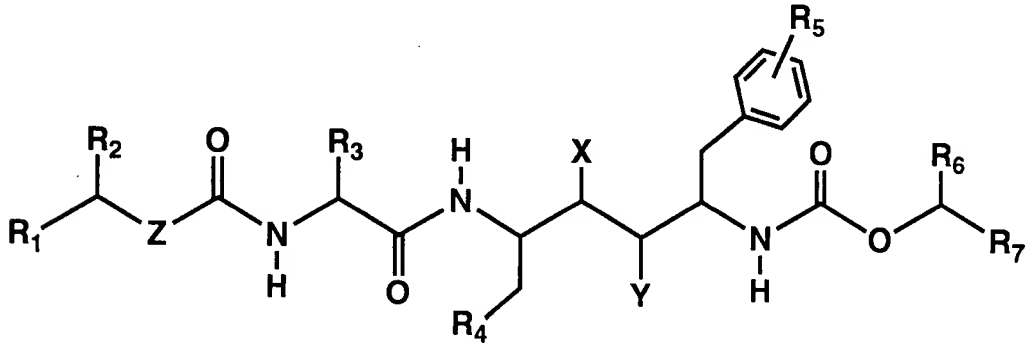
Even more preferred compounds of the formula **A** are those wherein R_1 is 2-monosubstituted-4-thiazolyl or 2-monosubstituted-4-oxazolyl wherein the substituent is loweralkyl; R_2 is hydrogen; R_4 is phenyl; R_5 is hydrogen; R_6 is hydrogen; R_7 is 5-thiazolyl, 5-oxazolyl, 5-isothiazolyl or 5-isoxazolyl; and Z is -O- or -N(R_8)- wherein R_8 is loweralkyl.

Most preferred compounds of the formula **A** are those wherein R_1 is 2-monosubstituted-4-thiazolyl or 2-monosubstituted-4-oxazolyl wherein the substituent is ethyl or isopropyl; R_2 is hydrogen; R_3 is methyl or isopropyl; R_4 is phenyl; R_5 is hydrogen; R_6 is hydrogen; R_7 is 5-thiazolyl, 5-oxazolyl, 5-isothiazolyl or 5-isoxazolyl; and Z is -O-.

Most preferred compounds of the formula **A** are also those wherein R_1 is 2-monosubstituted-4-thiazolyl or 2-monosubstituted-4-oxazolyl wherein the substituent is ethyl or isopropyl; R_2 is hydrogen; R_3 is isopropyl; R_4 is phenyl; R_5 is hydrogen; R_6 is hydrogen; R_7 is 5-thiazolyl, 5-oxazolyl, 5-isothiazolyl or 5-isoxazolyl; and Z is $-N(R_8)-$ wherein R_8 is methyl.

Most preferred compounds of the formula **A** are also those wherein configuration of the carbon atom bearing $-CH_2R_4$ is S and the configuration of the carbon bearing X is S when X is -OH and the configuration of the carbon atom bearing Y is S when Y is -OH and the configuration of the carbon atom bearing $-CH_2(R_5$-substituted phenyl) is S.

In accordance with the present invention, there are also retroviral protease inhibiting compounds of the formula **A1**:



A1

wherein R_1 is monosubstituted thiazolyl, monosubstituted oxazolyl, monosubstituted isoxazolyl or monosubstituted isothiazolyl wherein the substituent is selected from (i) loweralkyl, (ii) loweralkenyl, (iii) cycloalkyl, (iv)

cycloalkylalkyl, (v) cycloalkenyl, (vi)cycloalkenylalkyl, (vii) heterocyclic wherein the heterocyclic is selected from aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyridazinyl and pyrazinyl and wherein the heterocyclic is unsubstituted or substituted with a substituent selected from halo, loweralkyl, hydroxy, alkoxy and thioalkoxy, (viii) (heterocyclic)alkyl wherein heterocyclic is defined as above, (ix) alkoxyalkyl,
(x) thioalkoxyalkyl, (xi) alkylamino, (xii) dialkylamino, (xiii) phenyl wherein the phenyl ring is unsubstituted or substituted with a substituent selected from halo, loweralkyl, hydroxy, alkoxy and thioalkoxy, (xiv) phenylalkyl wherein the phenyl ring is unsubstituted or substituted as defined above,
(xv) dialkylaminoalkyl, (xvi) alkoxy and (xvii) thioalkoxy;

R_2 is hydrogen or loweralkyl;

R_3 is loweralkyl;

R_4 is phenyl, thiazolyl or oxazolyl wherein the phenyl, thiazolyl or oxazolyl ring is unsubstituted or substituted with a substituent selected from
(i) halo, (ii) loweralkyl, (iii) hydroxy, (iv) alkoxy and (v) thioalkoxy;

R_5 is hydrogen, halo, loweralkyl, hydroxy, alkoxy or thioalkoxy;

R_6 is hydrogen or loweralkyl;

R_7 is thiazolyl, oxazolyl, isoxazolyl or isothiazolyl wherein the thiazolyl, oxazolyl, isoxazolyl or isothiazolyl ring is unsubstituted or substituted with loweralkyl;

X is -OH and Y is -OH;

Z is -O-, -S-, -CH_2- or -N(R_8)- wherein R_8 is loweralkyl or cycloalkyl; or a pharmaceutically acceptable salt, ester or prodrug thereof.

Preferred compounds of the formula **A1** are those wherein R_1 is monosubstituted thiazolyl or monosubstituted oxazolyl; R_2 is hydrogen; R_4 is phenyl or thiazolyl; R_5 is hydrogen; R_6 is hydrogen and R_7 is thiazolyl, oxazolyl, isothiazolyl or isoxazolyl.

More preferred compounds of the formula **A1** are those wherein R_1 is 2-monosubstituted-4-thiazolyl or 2-monosubstituted-4-oxazolyl; R_2 is hydrogen; R_4 is phenyl; R_5 is hydrogen; R_6 is hydrogen and R_7 is 5-thiazolyl, 5-oxazolyl, 5-isothiazolyl or 5-isoxazolyl.

Even more preferred compounds of the formula **A1** are those wherein R_1 is 2-monosubstituted-4-thiazolyl or 2-monosubstituted-4-oxazolyl wherein the substituent is loweralkyl; R_2 is hydrogen; R_4 is phenyl; R_5 is hydrogen; R_6 is hydrogen; R_7 is 5-thiazolyl, 5-oxazolyl, 5-isothiazolyl or 5-isoxazolyl; and Z is -O- or -N(R_8)- wherein R_8 is loweralkyl.

Preferred compounds of the formula **A1** are also those wherein the configuration of the carbon atom bearing -CH_2R_4 is S and the configuration of the carbon atom bearing -CH_2(R_5-substituted phenyl) is S.

The compounds of the invention comprise asymmetrically substituted centers (i.e., asymmetrically substituted carbon atoms). Such centers can be mixtures of isomers or a single stereoisomer (i.e., asymmetric). Racemic mixtures, mixtures of diastereomers, as well as single diastereomers of the compounds of the invention are included in the present invention. The terms "S" and "R" configuration are as defined by the IUPAC 1974 Recommendations for Section E, Fundamental Stereochemistry, Pure Appl. Chem. (1976) 45, 13 - 30.

The terms "Val" and "Ala" as used herein refer to valine and alanine, respectively. Unless otherwise noted, when "Val" and "Ala" are used herein they refer to the L-isomer. In general, the amino acid abbreviations used herein

follow the IUPAC-IUB Joint Commission on Biochemical Nomenclature for amino acids and peptides (Eur. J. Biochem. 1984, 158, 9-31).

The term "N-protecting group" or "N-protected" as used herein refers to those groups intended to protect the N-terminus of an amino acid or peptide or to protect an amino group against undersirable reactions during synthetic procedures. Commonly used N-protecting groups are disclosed in Greene, "Protective Groups In Organic Synthesis," (John Wiley & Sons, New York (1981)), which is hereby incorporated by reference. N-protecting groups comprise carbamates, amides, N-alkyl derivatives, amino acetal derivatives, N-benzyl derivatives, imine derivatives, enamine derivatives and N-heteroatom derivatives. Preferred N-protecting groups are formyl, acetyl, benzoyl, pivaloyl, t-butylacetyl, phenylsulfonyl, benzyl, t-butyloxycarbonyl (Boc), benzyloxycarbonyl (Cbz) and the like.

The term "O-protecting group" as used herein refers to a substituent which protects hydroxyl groups against undesirable reactions during synthetic procedures such as those O-protecting groups disclosed in Greene, "Protective Groups In Organic Synthesis," (John Wiley & Sons, New York (1981)). O-protecting groups comprise substituted methyl ethers, for example, methoxymethyl, benzyloxymethyl, 2-methoxyethoxymethyl, 2-(trimethylsilyl)ethoxymethyl, t-butyl, benzyl and triphenylmethyl; tetrahydropyranyl ethers; substituted ethyl ethers, for example, 2,2,2-trichloroethyl; silyl ethers, for example, trimethylsilyl, t-butyldimethylsilyl and t-butyldiphenylsilyl; and esters prepared by reacting the hydroxyl group with a carboxylic acid, for example, acetate, propionate, benzoate and the like.

The term "loweralkyl" as used herein refers to straight or branched chain alkyl radicals containing from 1 to 6 carbon atoms including, but not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, n-pentyl, 1-methylbutyl, 2,2-dimethylbutyl, 2-methylpentyl, 2,2-dimethylpropyl, n-hexyl and the like.

The term "loweralkenyl" as used herein refers to a straight or branched chain alkyl radical containing from 2 to 6 carbon atoms and also having one

carbon-carbon double bond including, but not limited to, vinyl, 2-propenyl, 2-methyl-2-propenyl, 3-butenyl, 4-pentenyl, 5-hexenyl and the like.

The term "phenyl" as used herein refers to a phenyl group which is unsubstituted or substituted with a substituent selected from loweralkyl, alkoxy, thioalkoxy, hydroxy and halo.

The term "phenylalkyl" as used herein refers to an phenyl group appended to a loweralkyl radical including, but not limited to, benzyl, 4-hydroxybenzyl, 4-chlorobenzyl, 1-naphthylmethyl and the like.

The term "alkylamino" as used herein refers to a loweralkyl radical appended to an -NH radical.

The term "cycloalkyl" as used herein refers to an aliphatic ring having 3 to 7 carbon atoms including, but not limited to, cyclopropyl, cyclopentyl, cyclohexyl and the like. A preferred cycloalkyl group is cyclopropyl

The term "cycloalkylalkyl" as used herein refers to a cycloalkyl group appended to a loweralkyl radical, including but not limited to cyclohexylmethyl.

The term "cycloalkenyl" as used herein refers to to an aliphatic ring having 5 to 7 carbon atoms and also having one carbon-carbon double bond including, but not limited to, cyclopentenyl, cyclohexenyl and the like.

The term "cycloalkenyalkyl" as used herein refers to a cycloalkenyl group appended to a loweralkyl radical including, but not limited to, cyclopentenylmethyl, cyclhexenylmethyl and the like.

The terms "alkoxy" and "thioalkoxy" as used herein refer to $R_{15}O$- and $R_{15}S$-, respectively, wherein R_{15} is a loweralkyl group or benzyl.

The term "alkoxyalkyl" as used herein refers to an alkoxy group appended to a loweralkyl radical.

The term "thioalkoxyalkyl" as used herein refers to a thioalkoxy group appended to a loweralkyl radical.

The term "dialkylamino" as used herein refers to $-NR_{16}R_{17}$ wherein R_{16} and R_{17} are independently selected from loweralkyl groups.

The term "dialkylaminoalkyl" as used herein refers to $-NR_{18}R_{19}$ which is appended to a loweralkyl radical wherein R_{18} and R_{19} are independently selected from loweralkyl.

The term "halo" or "halogen" as used herein refers to -Cl, -Br, -I or -F.

The term "(heterocyclic)alkyl" as used herein refers to a heterocyclic group appended to a loweralkyl radical, including but not limited to pyrrolidinylmethyl and morpholinylmethyl.

In the compounds of the invention, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

Preferred compounds of the invention are selected from the group consisting of:

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)-amino)carbonyl)alaninyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

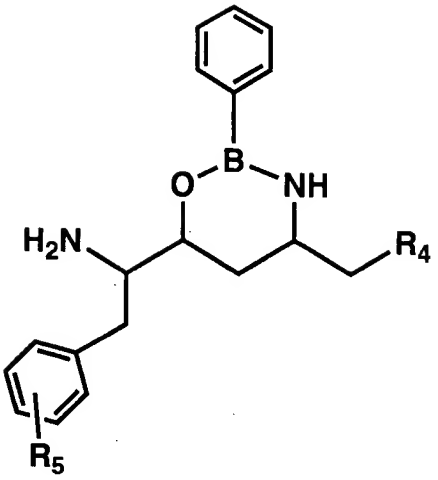
(2S,3S,5S)-2-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)valinyl)amino)-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)alaninyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((2-(N,N-Dimethylamino)-4-thiazolyl)methoxycarbonyl)-valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-2-(N-(N-((2-(N,N-Dimethylamino)-4-thiazolyl)methoxycarbonyl)-valinyl)amino)-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;
(2S,3S,5S)-5-(N-(N-((2-(4-Morpholinyl)-4-thiazolyl)methoxycarbonyl)-valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;
(2S,3S,5S)-2-(N-(N-((2-(4-Morpholinyl)-4-thiazolyl)-methoxycarbonyl)valinyl)-amino)-5-(N-((5-thiazolyl)-methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;
(2S,3S,5S)-5-(N-(N-((2-(1-Pyrrolidinyl)-4-thiazolyl)methoxycarbonyl)-valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;
(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;
(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;
(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;
(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane; and
(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane; or a pharmaceutically acceptable salt thereof.

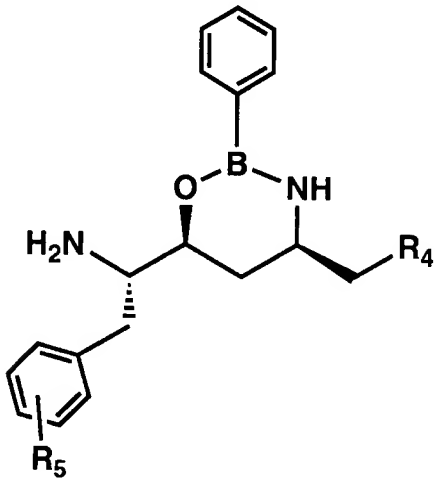
Compounds useful as intermediates for the preparation of the compound of formula **A** include the compound of the formula **A2:**



A2

wherein R_4 is phenyl, thiazolyl or oxazolyl wherein the phenyl, thiazolyl or oxazolyl ring is unsubstituted or substituted with a substituent selected from (i) halo, (ii) loweralkyl, (iii) hydroxy, (iv) alkoxy and (v) thioalkoxy; and R_5 is hydrogen, halo, loweralkyl, hydroxy, alkoxy or thioalkoxy; or an acid addition salt thereof.

Preferred intermediates of the formula **A2** are compounds of the formula:

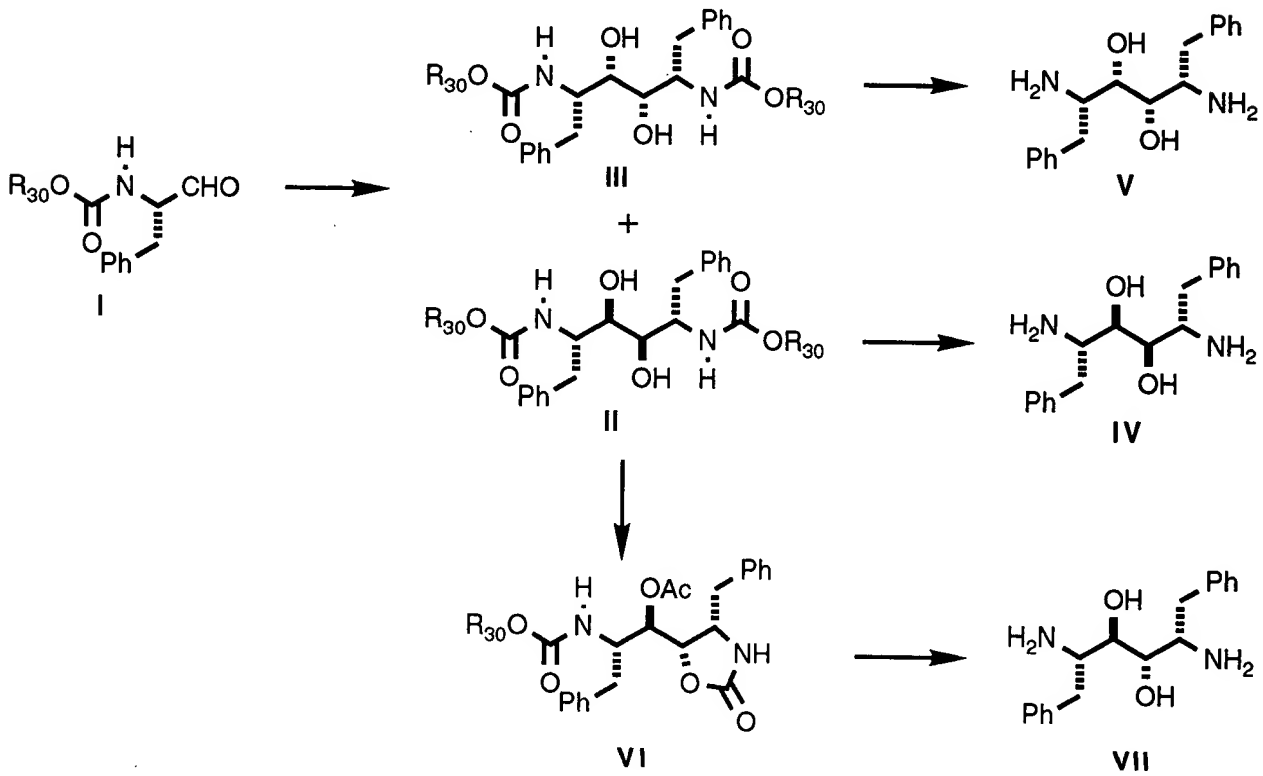


wherein R_4 is phenyl wherein the phenyl ring is unsubstituted or substituted with a substituent selected from (i) halo, (ii) loweralkyl, (iii) hydroxy, (iv) alkoxy

and (v) thioalkoxy; and R_5 is hydrogen, halo, loweralkyl, hydroxy, alkoxy or thioalkoxy; or an acid addition salt thereof.

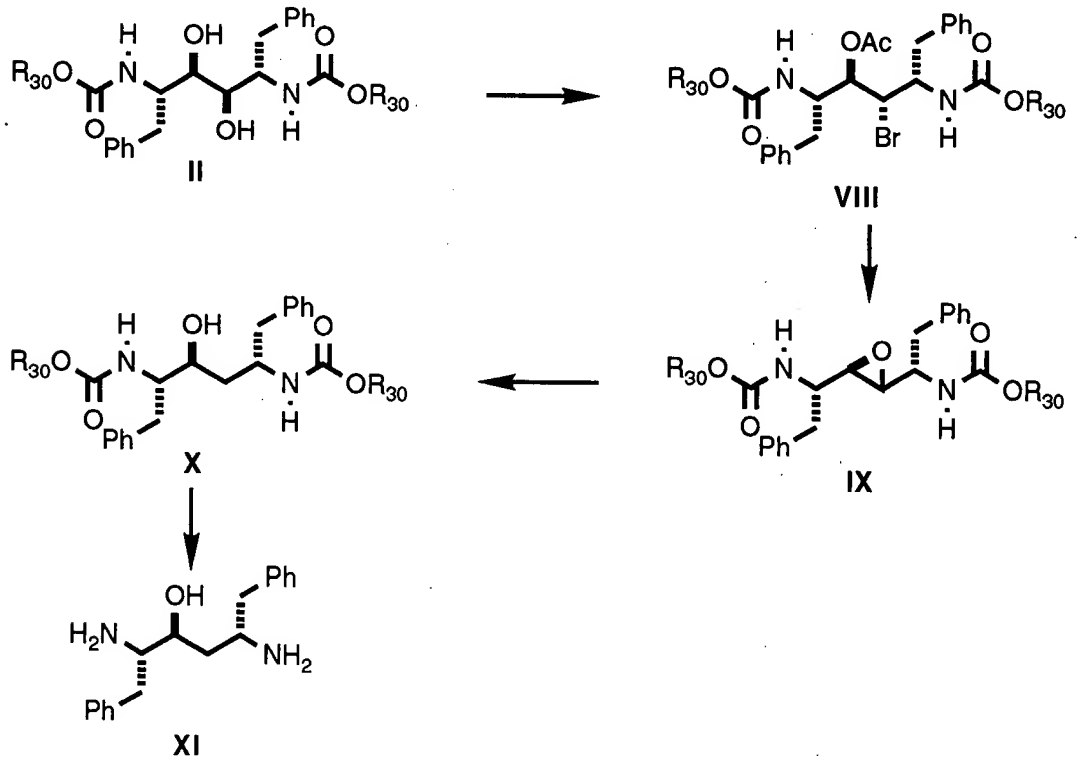
The compounds of the invention can be prepared as shown in Schemes 1 - 6. As outlined in Scheme 1, dimerization of protected α-aminoaldehyde **I** (R_{30} is loweralkyl or benzyl) with VCl_3(tetrahydrofuran)$_3$ and Zn produces a mixture of diols, out of which compounds **II** and **III** can be isolated. Hydrolysis of **II** and **III** with barium hydroxide leads, respectively, to diaminodiols **IV** and **V**. Alternately, treatment of **II** with α-acetoxyisobutyryl bromide in acetonitrile leads to compound **VI**, which upon hydrolysis with barium hydroxide, produces diaminodiol **VII**.

Scheme 1



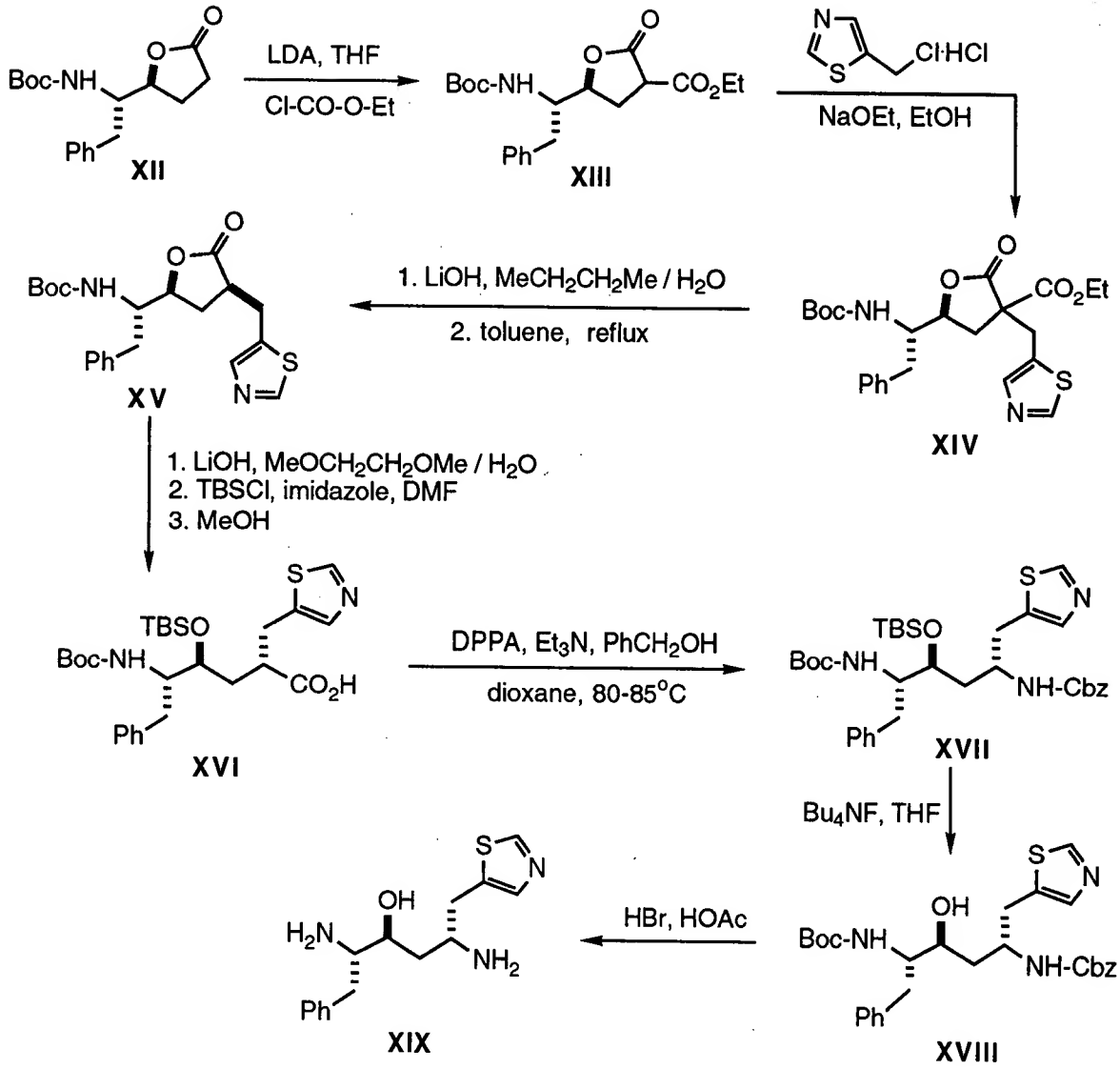
As outlined in Scheme 2, treatment of compound **II** with α-acetoxy-isobutyryl bromide in hexane/dichloromethane produces bromoacetate **VIII**. Hydrolysis of **VIII** with concommitant cyclization produces epoxide **IX**, which is reduced with sodium borohydride and trifluoroacetic acid to produce compound **X**. Barium hydroxide hydrolysis of **X** leads to diamine **XI**.

Scheme 2



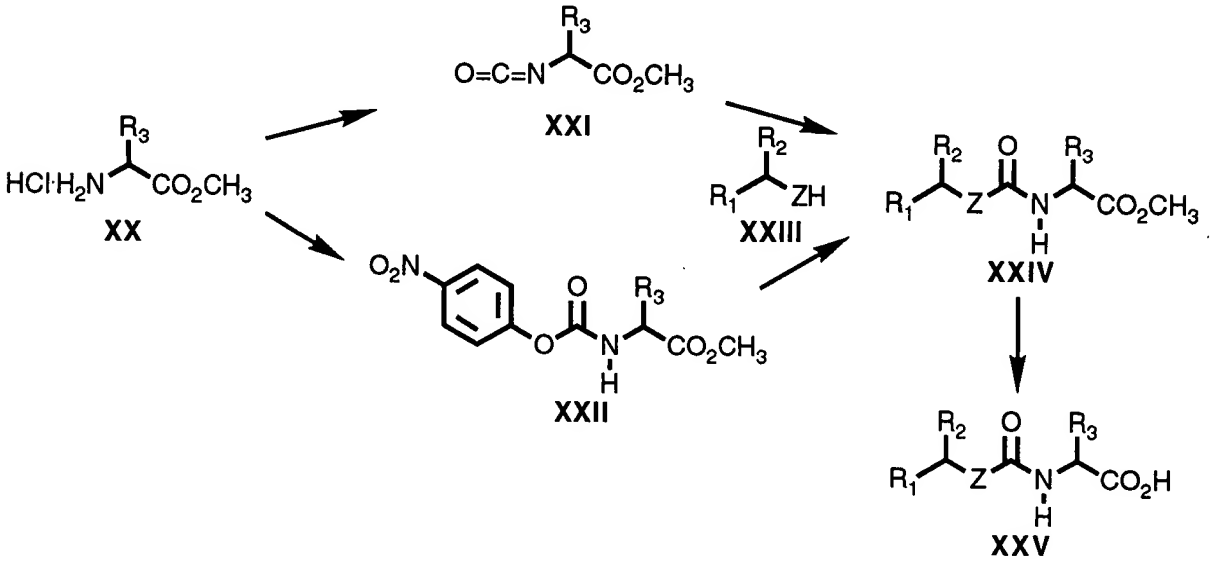
As outlined in Scheme 3, acylation of the enolate derived from compound **XII** with ethyl chloroformate gives compound **XIII**. Subsequent alkylation of the enolate prepared from **XIII** provides compound **XIV**, which is hydrolyzed and decarboxylated to lactone **XV**. Hydrolysis of **XV** and protection of the hydroxyl group leads to compound **XVI**, which, upon treatment with diphenylphosphoryl azide undergoes a Curtius rearrangement. The intermediate isocyanate is trapped with benzyl alcohol to produce compound **XVII**. Desilylation of **XVII** with tetrabutylammonium fluoride provides compound **XVIII**, which is deprotected with HBr to give diamine **XIX**.

Scheme 3


Boc-NH
Ph
XII
LDA, THF
Cl-CO-O-Et
CO2Et
XIII
Cl·HCl
NaOEt, EtOH
XIV
1. LiOH, MeCH2CH2Me / H2O
2. toluene, reflux
XV
1. LiOH, MeOCH2CH2OMe / H2O
2. TBSCl, imidazole, DMF
3. MeOH
TBSO
CO2H
XVI
DPPA, Et3N, PhCH2OH
dioxane, 80-85°C
NH-Cbz
XVII
Bu4NF, THF
OH
XVIII
HBr, HOAc
H2N
NH2
XIX

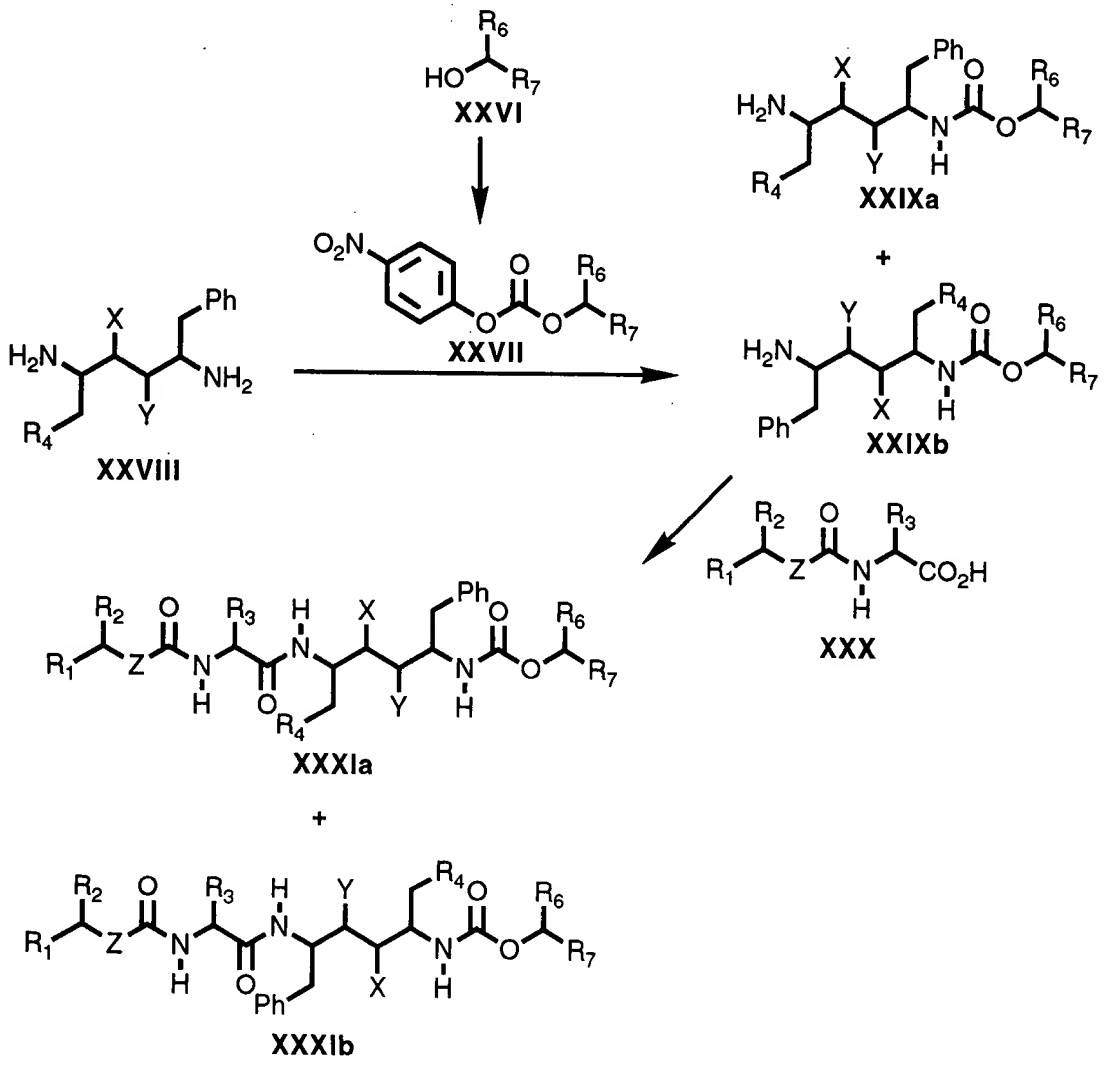
As outlined in Scheme 4, compound **XX** (R_3 is loweralkyl) is converted to isocyanate **XXI** by treatment with phosgene. Alternately, treatment of **XX** with 4-nitrophenyl chloroformate produces carbamate **XXII**. Condensation of either **XXI** or **XXII** with compound **XXIII**, with catalytic 4-dimethylaminopyridine as needed, provides compound **XXIV**. Lithium hydroxide hydrolysis of **XXIV** produces compound **XXV**.

Scheme 4



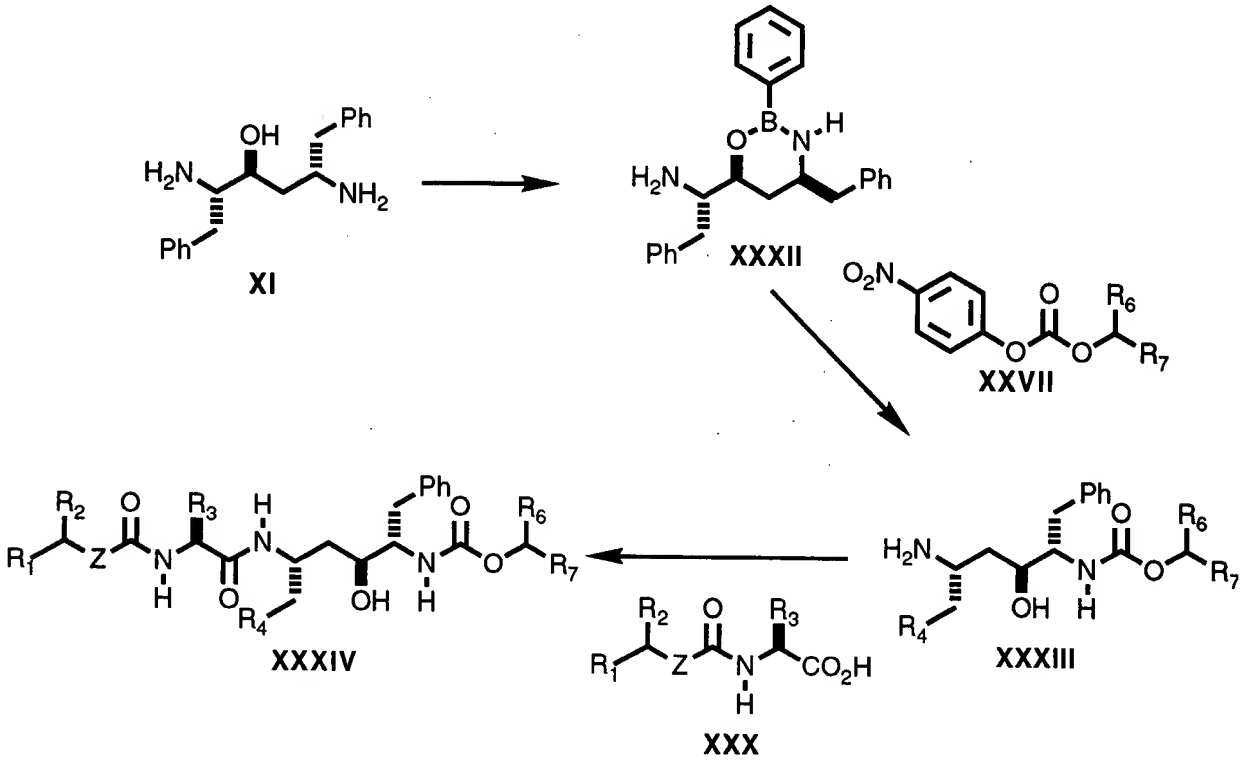
As outlined in Scheme 5, activation of compound **XXVI** with 4-nitrophenyl chloroformate provides compound **XXVII**. Compound **XXVIII**, which represents diamines **IV**, **V**, **VII**, **XI** and **XIX**, is acylated with **XXVII** to provide a mixture of compounds **XXIXa** and **XXIXb**. Coupling of **XXIXa** or **XXIXb** to compound **XXX** by treatment with a carbodiimide produces compound **XXXIa** or **XXXIb**, respectively.

Scheme 5



As outlined in Scheme 6, treatment of diamine **XI** with phenylboric acid produces compound **XXXII**, which is selectively acylated by compound **XXVII** to provide compound **XXIX**. Carbodiimide-mediated coupling of **XXXIX** to compound **XXX** leads to compound **XXXI**.

Scheme 6



The following examples will serve to further illustrate the preparation of the novel compounds of the invention.

Example 1

A. N-(((Benzyl)oxy)carbonyl)-L-phenylalaninal.

A solution of 24.5 ml of anhydrous dimethyl sulfoxide in 870 ml of anhydrous dichloromethane was cooled under N_2 atmosphere to -60°C and treated over a period of 15 min with 131 ml of a 2 M solution of oxalyl chloride in dichloromethane in order that the internal temperature remained below -

50°C. After addition, the solution was stirred at -60°C for 15 min and treated over a period of 20 min with a solution of 50 g (0.175 mol) of N-(((benzyl)oxy)-carbonyl)-L-phenylalaninol in 200 ml of dichloromethane. The resulting solution was stirred at -60°C for 1 h, then treated over a period of 15 min with 97 ml of triethylamine in order that the internal temperature remained below -50°C. After addition the solution was stirred at -60°C for 15 min, then, with the cooling bath in place, was treated rapidly (over a period of 1 min) with a solution of 163 g of citric acid in 550 ml of water. The resulting slurry was stirred vigorously for 10 min, allowed to warm, diluted to 1 liter with water, and separated. The organic layer was washed with 700 ml of water followed by a mixture of 550 ml of water and 150 ml of saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated in vacuo at 20°C to give the crude desired compound as a light yellow solid.

B. (2S,3R,4R,5S)-2,5-Bis-(N-(((benzyl)oxy)carbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane and (2S,3S,4S,5S)-2,5-Bis-(N-(((benzyl)oxy)carbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

A suspension of 78.5 g of VCl_3·(tetrahydrofuran)$_3$ and 16 g of zinc dust in 400 ml of dry dichloromethane was stirred under N_2 atmosphere for 1 h at 25°C. A solution of 0.175 mol of N-(((benzyl)oxy)carbonyl)-L-phenylalaninal in 200 ml of dichloromethane was then added in one portion, and the resulting mixture was stirred at ambient temperature under N_2 atmosphere for 16 h. The resulting mixture was added to 500 ml of 1 M aqueous HCl, diluted with 500 ml of hot chloroform, and shaked vigorously for 2 min. The layers were separated, and the organic layer was washed with 1 M aqueous HCl and separated. Filtration of the organic phase provided the crude desired product as a solid residue. The residue was slurried in 1.25 liters of acetone, treated with 5 ml of concentrated H_2SO_4, and stirred for 16 h at ambient temperature. The resulting mixture was filtered, and the residue (residue A) was washed with 50 ml of acetone. The combined filtrate was concentrated to a volume of 250 ml, diluted with 1000 ml of dichloromethane, washed three times with water and

once with saturated brine, dried over $MgSO_4$, and concentrated to give a viscous oil. The oil was taken up in 1000 ml of 1 M HCl in methanol (prepared from 71 ml of acetyl chloride and 1000 ml of methanol) and stirred at ambient temperature for 2 h. The resulting precipitate was filtered, washed with methanol, and air-dried on the filter to provide 26.7 g of the desired compound as a white solid. The filtrate was concentrated and filtered to give a second crop (8.3 g) of (2S,3R,4R,5S)-2,5-bis-(N-(((benzyl)oxy)carbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane. ^1H NMR (d_6-DMSO) δ 2.59 (dd, J = 13, 5 Hz, 2 H), 2.74 (dd, J = 13, 9 Hz, 2 H), 3.26 (br, 2 H), 4.19 (m, 2 H), 4.54 (m, 2 H), 4.92 (m, 4 H), 6.82 (d, J = 9 Hz, 2 H), 7.0-7.35 (m, 20 H). Mass spectrum: $(M + H)^+$ = 569.

Residue A (above, 2.65 g) was suspended in 75 ml of tetrahydrofuran (THF) and 75 ml of 1 M aqueous HCl and heated at reflux for 24 h. After concentration of the resulting solution in vacuo, the residue was taken up in 10% methanol in chloroform, washed two times with water, dried over Na_2SO_4, and concentrated in vacuo to provide (2S,3S,4S,5S)-2,5-bis-(N-(((benzyl)oxy)carbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane as a white solid. ^1H NMR (d_6-DMSO) δ 2.64 (m, 2 H), 3.04 (m, 2 H), 3.49 (m, 2 H), 3.78 (m, 2 H), 4.70 (d, J = 7 Hz, 2 H), 4.93 (AA', 4 H), 7.1-7.4 (m, 20 H). Mass spectrum: $(M + H)^+$ = 569.

C. (2S,3R,4S,5S)-3-Acetoxy-2,5-bis-(N-(((benzyl)oxy)carbonyl)amino)-3-bromo-1,6-diphenylhexane.

A suspension of 25 g (44 mmol) of (2S,3R,4R,5S)-2,5-bis-(N-(((benzyl)oxy)carbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane in 500 ml of 2:1 dichloromethane/hexane was treated with 23 g of a-acetoxyisobutyryl bromide. The resulting mixture was stirred at ambient temperature until the reaction clarified, washed with two 200 ml portions of saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated in vacuo to give 30.8 g of the crude desired compound. A portion was purified by silica gel chromatography using 9:1 dichloromethane:ethyl acetate to provide the pure desired compound

as a white solid. ^{1}H NMR ($CDCl_3$) δ 2.21 (s, 3 H), 2.62 (dd, J = 13, 11 Hz, 1 H), 2.75 (d, J = 7 Hz, 2 H), 2.95 (br d, J = 15 Hz, 1 H), 4.03 (br t, J = 10 Hz, 1 h), 4.40 (br d, J = 10 Hz, 1 H), 4.6-5.0 (m, 6 H), 5.12 (br d, J = 13 Hz, 1 H), 5.33 (br d, J = 11 Hz, 1 H), 7.0-7.4 (m, 10 H). Mass spectrum: $(M + NH_4)^+$ = 690, 692.

D. (2S,3R,4R,5S)-2,5-Bis-(N-(((benzyl)oxy)carbonyl)amino)-3,4-epoxy-1,6-diphenylhexane.

A solution of 35.56 g (52.8 mmol) of (2S,3R,4S,5S)-3-acetoxy-2,5-bis-(N-(((benzyl)oxy)carbonyl)amino)-3-bromo-1,6-diphenylhexane in 375 ml of dioxane was treated with 255 ml of 1N aqueous sodium hydroxide and stirred at ambient temperature for 16 h, during which the desired compound precipitated. The resulting mixture was filtered, and the residue was washed with water and dried to provide 22.23 g (76%) of the desired compound as a white solid. ^{1}H NMR ($CDCl_3$) δ 2.7-2.9 (m, 6 H), 3.9-4.0 (m, 2 H), 4.6-4.7 (m, 2 H), 5.03 (m, 4 H), 7.1-7.4 (m, 10 H).

E. (2S,3S,5S)-2,5-Bis-(N-(((benzyl)oxy)carbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

A mixture of 39.2 g (71.2 mmol) of (2S,3R,4R,5S)-2,5-bis-(N-(((benzyl)oxy)carbonyl)amino)-3,4-epoxy-1,6-diphenylhexane in 600 ml of THF was treated under N_2 atmosphere with 13 g (0.36 mol) of sodium borohydride. The resulting mixture was treated dropwise with 27.7 ml (0.36 mol) of trifluoroacetic acid. After being stirred for 3.5 h at ambient temperature, the resulting mixture was quenched with 1N aqueous HCl, diluted with water, and stirred for 16 h. The resulting mixture was filtered. washed with water, and dried to provide 22.85 g (58%) of the desired compound as a white solid.

F. (2S,3S,5S)-2,5-Diamino-1,6-diphenyl-3-hydroxyhexane.

A suspension of 32 g of the crude resultant compound of Example 1E and 55.5 g (176 mmol) of barium hydroxide octahydrate in 400 ml of 1,4-dioxane and 400 ml of water was heated at reflux for 4 h. The resulting mixture

was filtered, and the residue was rinsed with dioxane. The combined filtrates were concentrated to a volume of approximately 200 ml and extracted with four 400 ml portions of chloroform. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography using first 2% isopropylamine in chloroform and then 2% isopropylamine/2% methanol in chloroform to provide 10.1 g (81%) of the pure desired compound as a white solid. ^1H NMR ($CDCl_3$) δ 1.54 (dt, J = 14, 10 Hz, 1 H), 1.67 (dt, J = 14, 3 Hz, 1 H), 2.50 (dd, J = 13, 8 Hz, 1 H), 2.58 (dd, J = 13, 8 Hz, 1 H), 2.8 (m, 2 H), 2.91 (dd, J = 13, 5 Hz, 1 H), 3.10 (m, 1 H), 3.72 (ddd, J = 11, 3, 2 Hz, 1 H), 7.1-7.4 (m, 10 H). Mass spectrum: $(M + H)^+ = 285$.

G. (4S,6S,1'S)-6-(1-Amino-2-phenylethyl)-4-benzyl-2-phenyl-3-aza-2-bora-1-oxacyclohexane.

A solution of 11.28 g (40 mmol) of (2S,3S,5S)-2,5-diamino-1,6-diphenyl-3-hydroxyhexane and 4.88 g (40 mmol) of phenylboric acid in 1 liter of toluene was heated at reflux and the water azeotropically removed with the aid of a Dean Stark trap until the distillate was clear. The solvent was then removed in vacuo to provide the crude desired compound which was used immediately without further purification.

H. Thioformamide.

To a cooled (0°C) 2 L three neck round bottom flask equipped with an overhead stirrer charged with a solution of formamide (30.5 mL, 0.76 mol) in 1 L of diethyl ether was added 89 g (0.19 mol) of phosphorous pentasulfide in small portions. The reaction mixture was allowed to warm to ambient temperature, stirred for 2 h, filtered, and concentrated in vacuo to afford thioformamide as a yellow offensive smelling oil which was used without purification.

I. Ethyl 2-Chloro-2-formylacetate.

To a three neck 2 L round bottom flask charged with potassium t-butoxide (0.5 mol, 500 mL of a 1 M solution in THF) and 500 mL of dry THF cooled to 0°C was added dropwise from an addition funnel a solution of ethyl chloroacetate (0.5 mol, 53.5 mL) and ethyl formate (0.5 mol, 40.4 mL), in 200 mL of THF over 3 hours. After completion of addition, the reaction mixture was stirred for 1 hour and allowed to stand overnight. The resulting solid was diluted with diethyl ether and cooled in an ice bath. Then, the pH was lowered to approximately 3 using 6N HCl. The organic phase was separated, and the aqueous layer was washed 3 times with diethyl ether. The combined ethereal portions were dried over $NaSO_4$, and concentrated in vacuo. The crude desired compound was stored at -30°C and used without further purification.

J. Ethyl Thiazole-5-carboxylate.

To a round bottom flask was added 250 mL of dry acetone, 7.5 g (0.123 mol) of thioformamide, and 18.54 g (0.123 mol) of ethyl 2-chloro-2-formylacetate. The reaction was heated at reflux for 2 hours. The solvent was removed in vacuo, and the residue was purified by chromatography (SiO_2, 6 cm o.d. column, 100% $CHCl_3$, R_f = 0.25) to provide 11.6 g (60%) of the desired compound as a light yellow oil. NMR ($CDCl_3$) δ 1.39 (t, J = 7 Hz, 3 H), 4.38 (q, J = 7 Hz, 2 H), 8.50 (s, 1 H), 8.95 (s, 1 H).

K. 5-(Hydroxymethyl)thiazole.

To a precooled (ice bath) three neck 500 mL flask containing lithium aluminum hydride (76 mmol) in 250 mL of THF was added ethyl thiazole-5-carboxylate (11.82 g, 75.68 mmol) in 100 mL of THF dropwise over 1.5 hours to avoid excess foaming. The reaction was stirred for an additional hour, and treated cautiously with 2.9 mL of water, 2.9 mL of 15% NaOH, and 8.7 mL of water. The solid salts were filtered, and the filtrate set aside. The crude salts were heated at reflux in 100 mL of ethyl acetate for 30 min. The resulting mixture was filtered, and the two filtrates were combined, dried over Na_2SO_4,

and concentrated in vacuo. The product was purified by silica gel chromatography eluting sequentially with 0% - 2% - 4% methanol in chloroform, to provide the desired compound, Rf = 0.3 (4% methanol in chloroform), which solidified upon standing in 75% yield. NMR ($CDCl_3$) δ 4.92 (s, 2 H), 7.78 (s, 1 H), 8.77 (s, 1 H). Mass spectrum: $(M + H)^+ = 116$.

L. ((5-Thiazolyl)methyl)-(4-nitrophenyl)carbonate.

A solution of 3.11 g (27 mmol) of 5-(hydroxymethyl)thiazole and excess N-methyl morpholine in 100 ml of methylene chloride was cooled to 0°C and treated with 8.2 g (41 mmol) of 4-nitrophenyl chloroformate. After being stirred for 1 h, the reaction mixture was diluted with $CHCl_3$, washed successively with 1N HCl, saturated aqueous $NaHCO_3$, and saturated brine, dried over $NaSO_4$, and concentrated in vacuo. The residue was purified by silica gel chromatography (SiO2, 1-2% MeOH/$CHCl_3$, Rf=0.5 in 4% MeOH/$CHCl_3$) to yield 5.9 g (78%) of the desired compound as a yellow solid. NMR ($CDCl_3$) δ 5.53 (s, 2 H), 7.39 (dt, J = 9, 3 Hz, 2 H), 8.01 (s, 1 H), 8.29 (dt, J = 9, 3 Hz, 2 H), 8.90 (s, 1 H). Mass spectrum: $(M + H)^+ = 281$.

M. (2S,3S,5S)-5-Amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane and (2S,3S,5S)-2-Amino-5-(N-((5-thiazolyl)-methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

A solution of 500 mg (1.76 mmol) of (2S,3S,5S)-2,5-diamino-1,6-diphenyl-3-hydroxyhexane and 480 mg (1.71 mmol) of ((5-thiazolyl)methyl)-(4-nitrophenyl)carbonate in 20 ml of THF was stirred at ambient temperature for 4 h. After removal of the solvent in vacuo, the residue was purified by silica gel chromatography using first 2% then 5% methanol in chloroform to provide a mixture of the two desired compounds. Silica gel chromatography of the mixture using a gradient of 0 - 1 - 2% methanol in 93:2 isopropylamine: chloroform provided 110 mg (16%) of (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl)-methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane (R_f 0.48, 96:2:2 chloroform:methanol:isopropylamine) and 185 mg (28%) of (2S,3S,5S)-2-

amino-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane (R_f 0.44, 96:2:2 chloroform:methanol:isopropylamine).

(2S,3S,5S)-5-Amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane: NMR ($CDCl_3$) δ 1.3-1.6 (m, 2 H), 2.40 (dd, J = 14, 8 Hz, 1 H), 2.78 (dd, J = 5 Hz, 1 H), 2.88 (d, J = 7 Hz, 2 H), 3.01 (m, 1 H), 3.72 (br q, 1 H), 3.81 (br d, J = 10 Hz, 1 H), 5.28 (s, 2 H), 5.34 (br d, J = 9 Hz, 1 H), 7.07 (br d, J = 7 Hz, 2 H), 7.15 - 7.35 (m, 8 H), 7.87 (s, 1 H), 8.80 (s, 1 H). Mass spectrum: $(M + H)^+ = 426$.

(2S,3S,5S)-2-Amino-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane: NMR ($CDCl_3$) δ 1.55 (dt, J = 14, 8 Hz, 1 H), 1.74 (m, 1 H), 2.44 (dd, J = 15, 1 Hz, 1 H), 2.75 - 3.0 (m, 4 H), 3.44 (m, 1 H), 4.00 (br t, 1 H), 5.28 (m, 3 H), 7.1 - 7.4 (m, 10 H), 7.86 (s, 1 H), 8.80 (s, 1 H). Mass spectrum: $(M + H)^+ = 426$.

N. (2S,3S,5S)-5-Amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

A solution of 40 mmol of crude (4S,6S,1'S)-6-(1-amino-2-phenylethyl)-4-benzyl-2-phenyl-3-aza-2-bora-1-oxacyclohexane in 700 ml of anhydrous THF was cooled to -40°C and treated dropwise over a period of 1 h with a solution of 7.83 g (27.9 mmol) of ((5-thiazolyl)methyl)-(4-nitrophenyl)carbonate in 300 ml of dry THF. The resulting solution was allowed to warm to 0°C for 3 h, then to ambient temperature for 16 h. The solvent was removed in vacuo, and the residue was taken up in 700 ml of ethyl acetate, washed with three 150 ml portions of 1N aqueous NaOH and one 150 ml portion of brine. The organic phase was dried over Na_2SO_4 and concentrated in vacuo. Purification of the residue by silica gel chromatography using methanol/chloroform mixtures provided the desired compound mixed with its regioisomer. A second chromatography using 1-3% isopropylamine in chloroform provided 5.21 g of the desired compound which solidified upon standing.

O. 2-Methylpropane-thioamide.

A suspension of 100 g (1.15 mol) of isobutyramide in 4 L of diethyl ether was stirred vigorously and treated in portions with 51 g (0.115 mol) of P_4S_{10}. The resulting mixture was stirred at ambient temperature for 2 h, filtered, and concentrated in vacuo to provide 94.2 g (80%) of the crude desired compound. ^1H NMR (DMSO-d_6) δ 1.08 (d, J = 7 Hz, 6 H), 2.78 (heptet, J = 7 Hz, 1 H), 9.06 (br, 1 H), 9.30 (br, 1 H). Mass spectrum: $(M + H)^+ = 104$.

P. 4-(Chloromethyl)-2-isopropylthiazole hydrochloride.

A mixture of 94.0 g (0.91 mol) of 2-methylpropane-thioamide, 115.7 g (0.91 mol) of 1,3-dichloroacetone, and 109.7 g (0.91 mol) of $MgSO_4$ in 1.6 liters of acetone was heated at reflux for 3.5 h. The resulting mixture was allowed to cool, filtered, and the solvent was removed in vacuo to provide the crude desired compound as a yellow oil. ^1H NMR (DMSO-d_6) δ 1.32 (d, J = 7 Hz, 6 H), 3.27 (heptet, J = 7 Hz, 1 H), 4.78 (s, 2 H), 7.61 (s, 1 H). Mass spectrum: $(M + H)^+ = 176$.

Q. 2-Isopropyl-4-(((N-methyl)amino)methyl)thiazole.

A solution of 40 g of 4-(chloromethyl)-2-isopropylthiazole hydrochloride in 100 ml of water was added dropwise with stirring to 400 ml of 40% aqueous methylamine. The resulting solution was stirred for 1 h, then concentrated in vacuo. The residue was taken up in chloroform, dried over Na_2SO_4, and concentrated in vacuo. Purification of the residue by silica gel chromatography using 10% methanol in chloroform provided 21.35 g (55%) of the desired compound. ^1H NMR (DMSO-d_6) δ 1.34 (d, J = 7 Hz, 6 H), 2.56 (s, 3 H), 3.30 (heptet, J = 7 Hz, 1 H), 4.16 (s, 2 H), 7.63 (s, 1 H). Mass spectrum: $(M + H)^+ = 171$.

R. N-(((4-Nitrophenyl)oxy)carbonyl)-L-valine Methyl Ester.

A solution of 66.1 g (0.328 mol) of 4-nitrophenyl chloroformate in 1.2 liters of CH_2Cl_2 was cooled to 0°C and treated with L-valine methyl ester hydrochloride. The resulting mixture was treated slowly, with stirring, with 68.9 ml (0.626 mol) of 4-methylmorpholine. The resulting solution was allowed to slowly warm to ambient temperature and was stirred overnight. After washing with 3 portions of 10% aqueous $NaHCO_3$, the solution was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel chromatography by eluting with chloroform to provide the desired compound. ^1H NMR (DMSO-d_6) δ 0.94 (d, J = 7 Hz, 3 H), 0.95 (d, J = 7 Hz, 3 H), 2.12 (octet, J = 7 Hz, 1 H), 3.69 (s, 3 H), 4.01 (dd, J = 8, 6 Hz, 1 H), 7.41 (dt, J = 9, 3 Hz, 2 H), 8.27 (dt, J = 9, 3 Hz, 2 H), 8.53 (d, J = 8 Hz, 1 H). Mass spectrum: $(M + NH_4)^+$ = 314.

S. N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine Methyl Ester.

A solution of 15.7 g (92 mmol) of 2-isopropyl-4-(((N-methyl)amino)-methyl)thiazole in 200 ml of THF was combined with a solution of 20.5 g (69 mmol) of N-(((4-nitrophenyl)oxy)carbonyl)-L-valine methyl ester. The resulting solution was treated with 1.6 g of 4-dimethylaminopyridine and 12.9 ml (92 mmol) of triethylamine, heated at reflux for 2 h, allowed to cool, and concentrated in vacuo. The residue was taken up in CH_2Cl_2, washed extensively with 5% aqueous K_2CO_3, dried over Na_2SO_4, and concentrated in vacuo. The resulting product mixture was purified by silica gel chromatography using chloroform as an eluent to provide 16.3 g (54%) of the desired compound. ^1H NMR (DMSO-d_6) δ 0.88 (d, J = 7 Hz, 3 H), 0.92 (d, J = 7 Hz, 3 H), 1.32 (d, J = 7 Hz, 3 H), 2.05 (octet, J = 7 Hz, 1 H), 2.86 (s, 3 H), 3.25 (heptet, J = 7 Hz, 1 H), 3.61 (s, 3 H), 3.96 (dd, J = 8, 7 Hz, 1 H), 4.44 (AA', 2 H), 6.58 (d, J = 8 Hz, 1 H), 7.24 (s, 1 H). Mass spectrum: $(M + H)^+$ = 328.

T. N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine.

A solution of 1.42 g (4.3 mmol) of the resultant compound of Example 1S in 17 ml of dioxane was treated with 17.3 ml of 0.50 M aqueous LiOH. The resulting solution was stirred at ambient temperature for 30 min, treated with 8.7 ml of 1 M HCl, and concentrated in vacuo. The residue was taken up in dichloromethane, washed with water, dried over Na_2SO_4, and concentrated in vacuo to provide 1.1 g (81%) of the desired compound. Mass spectrum: $(M + H)^+ = 314$.

U. (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

A solution of 70 mg (0.223 mmol) of N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine, 79 mg (0.186 mmol) of (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane, 30 mg (0.223 mmol) of 1-hydroxybenzotriazole hydrate, and 51 mg (0.266 mmol) of N-ethyl-N'-dimethylaminopropyl carbodiimide in 2 ml of THF was stirred at ambient temperature for 16 h. The resulting solution was concentrated in vacuo, and the residue was purified by silica gel chromatography using 97:3 CH_2Cl_2:CH_3OH to provide 100 mg (74%) of the desired compound (R_f 0.4, 95:5 CH_2Cl_2:CH_3OH) as a solid, mp 61-63°C. Mass spectrum: $(M + H)^+ = 721$. Anal. Calcd for $C_{37}H_{49}N_6O_5S_2 \cdot 0.5H_2O$: C, 60.88; H, 6.77; N, 11.51. Found: C, 60.68; H, 6.53; N, 11.36.

Example 2

Following the procedures of Example 1, the following compounds can be prepared:

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-cyclopentyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-cyclohexyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1,1-dimethyl)ethyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-cyclobutyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-cyclopropyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-ethyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-ethenyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-propenyl)-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-cyclopentenyl)-4-thiazolyl)-methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)-methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-cyclohexenyl)-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((4-cyclopentenyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((4-cyclohexenyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(3-propenyl)-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-propenyl)-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-methyl-1-propenyl)-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-methyl-1-propenyl)-4-thiazolyl)-methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)-amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1,2-dimethyl-1-propenyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)-methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(cyclopentyl)methyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(cyclohexyl)methyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-phenyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-benzyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-phenyl)ethyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-phenyl-1-ethenyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)-methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(4-fluoro)phenyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-chloro)phenyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(3-methoxy)phenyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-thiazolyl)-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-thiazolyl)methyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-methoxy-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-ethoxy-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyloxy-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(N,N-dimethylamino)methyl-4-thiazolyl)-methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)-amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-pyrrolidinyl)methyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-propyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-methyl)propyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-methyl)propyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-ethyl)propyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Example 3.

A. N-(((4-nitrophenyl)oxy)carbonyl)-L-alanine Methyl Ester.

Using the procedure of Example 1R, but replacing L-valine methyl ester hydrochloride with L-alanine methyl ester hydrochloride provided the desired compound (R_f 0.25, dichloromethane) in 95% yield.

B. N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-alanine Methyl Ester.

Using the procedure of Example 1S, but replacing N-(((4-nitrophenyl)oxy)carbonyl)-L-valine methyl ester with the resultant compound of Example 3A provided, after silica gel chromatography using 97:3 CH_2Cl_2:CH_3OH, the desired compound (R_f 0.55, 95:5 CH_2Cl_2: CH_3OH) in 24% yield. ^1H NMR ($CDCl_3$) δ 1.39 (d, J = 7 Hz, 6 H), 1.43 (d, J = 7 Hz, 3 H), 2.98 (s, 3 H), 3.28 (heptet, J = 7 Hz, 1 H), 3.74 (s, 3 H), 4.46 (s, 2 H), 4.49 (q, J = 7 Hz, 1 H), 6.12 (br, 1 H), 6.98 (s, 1 H). Mass spectrum: $(M + H)^+ = 300$.

C. N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-alanine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 3B provided the desired compound.

D. (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)alaninyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with the resultant compound of Example 3C provided, after silica gel chromatography using 97:3 CH_2Cl_2:CH_3OH, 70 mg (35%) of the desired compound (R_f 0.36, 95:5 CH_2Cl_2:CH_3OH), mp. 56-58°C. Mass spectrum: $(M + H)^+ = 693$. Anal. Calcd for $C_{35}H_{44}N_6O_5S_2 \cdot 0.5H_2O$: C, 59.89; H, 6.46; N, 11.97. Found: C, 60.07; H, 6.39; N, 12.00.

Example 4

A. 2-Isopropyl-4-(((N-ethyl)amino)methyl)thiazole.

Using the procedure of Example 1Q, but replacing 40% aqueous methylamine with 70% aqueous ethylamine provided the crude desired

compound. ^{1}H NMR (DMSO-d_6) δ 1.12 (t, J = 7 Hz, 3 H), 1.32 (d, J = 7 Hz, 6 H), 2.78 (q, J = 7 Hz, 2 H), 3.27 (q, J = 7 Hz, 1 H), 3.97 (s, 2 H), 7.44 (s, 1 H).

B. N-((N-Ethyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine Methyl Ester.

Using the procedure of Example 1S, but replacing N-(((4-nitrophenyl)oxy)carbonyl)-L-valine methyl ester with the resultant compound of Example 4A provided, after silica gel chromatography using 98:2 $CHCl_3$:CH_3OH, the desired compound (R_f 0.5, 95:3 CH_2Cl_2:CH_3OH) in 54% yield. ^{1}H NMR ($CDCl_3$) δ 0.94 (d, J = 7 Hz, 3 H), 0.98 (d, J = 7 Hz, 3 H), 1.16 (t, J = 7 Hz, 3 H), 1.39 (d, J = 7 Hz, 6 H), 2.16 (m, 1 H), 3.25 - 3.50 (m, 3 H), 3.71 (s, 3 H), 4.38 (dd, J = 8, 6 Hz, 1 H), 4.46 (AA', 2 H), 6.13 (br, 1 H), 7.00 (s, 1 H). Mass spectrum: $(M + H)^+$ = 342.

C. N-((N-Ethyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 4B provided the desired compound.

D. (2S,3S,5S)-5-(N-(N-((N-Ethyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with the resultant compound of Example 4C provided, after silica gel chromatography using 98:2 $CHCl_3$:CH_3OH, 60 mg (35%) of the desired compound (R_f 0.4, 95;5 CH_2Cl_2:CH_3OH), mp. 58-60°C. Mass spectrum: $(M + H)^+$ = 735.

Example 5

A. Ethyl 2-isopropyl-4-thiazole Carboxylate.

A solution of 2.35 g (23 mmol) of 2-methylpropane-thioamide and 2.89 ml (23 mmol) of ethyl bromopyruvate in 75 ml of acetone was treated with excess $MgSO_4$ and heated at reflux for 2.5 h. The resulting mixture was allowed to cool, filtered, and concentrated in vacuo to an oil, which was taken up in chloroform, washed sequentially with aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated. The residue was purified by chromatography on silica gel using chloroform as an eluent to provide 3.96 g (86%) of the desired compound, R_f 0.21 (chloroform) as an oil. ^1H NMR ($CDCl_3$) δ 1.41 (t, J = 8 Hz, 3 H), 1.42 (d, J = 7 Hz, 6 H), 3.43 (heptet, J = 7 Hz, 1 H), 4.41 (q, J = 8 Hz, 2 H), 8.05 (s, 1 H). Mass spectrum: $(M + H)^+ = 200$.

B. 4-(Hydroxymethyl)-2-isopropylthiazole.

A solution of 10 ml (10 mmol) of lithium aluminum hydride in toluene was diluted in a dry flask under N_2 atmosphere with 75 ml of THF. The resulting mixture was cooled to 0°C and treated dropwise with a solution of 3.96 g (20 mmol) of ethyl 2-isopropyl-4-thiazolecarboxylate in 10 ml of THF. After addition, the solution was stirred at 0°C for 3 h, diluted with ether, and treated with a small amount of aqueous Rochelle's salt. After stirring, the slurry was filtered, washed with ethyl acetate, and the combined filtrates were concentrated in vacuo. The residue was purified by silica gel chromatography using 2% methanol in chloroform to provide 2.18 g (69%) of the desired compound, R_f 0.58 (4% methanol in chloroform). ^1H NMR ($CDCl_3$) δ 1.39 (d, J = 7 Hz, 6 H), 2.94 (br, 1 H), 3.31 (heptet, J = 7 Hz, 1 H), 4.74 (s, 2 H), 7.04 (s, 1 H). Mass spectrum: $(M + H)^+ = 158$.

C. α-Isocyanato-valine Methyl Ester.

A suspension of L-valine methyl ester hydrochloride (49 g, 0.29 mol) in toluene (700 ml) was heated to 100°C and phosgene gas was bubbled into the reaction mixture. After approximately 6 h, the mixture became

homogeneous. The bubbling of phosgene was continued for 10 more min, then the solution was cooled with the bubbling of N_2 gas. The solvent was then evaporated and the residue chased with toluene two times. Evaporation of solvent gave 40.8 g (89%) of the crude desired compound.

D. N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)valine Methyl Ester.

A solution of 2.18 g (15 mmol) of 4-(hydroxymethyl)-2-isopropylthiazole, 15.8 mmol of α-isocyanato-valine methyl ester and 1.5 mmol of 4-dimethylaminopyridine in 75 ml of dichloromethane was heated at reflux for 5 h. The resulting solution was washed successively with 10% citric acid, aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated in vacuo. Silica gel chromatography of the residue using 5% ethyl acetate in chloroform provided 2.67 g (57%) of the pure desired compound, R_f 0.46 (4% methanol in chloroform). NMR ^1H NMR (DMSO-d_6) δ 1.26 (d, J = 8 Hz, 3 H), 1.32 (d, J = 7 Hz, 6 H), 3.27 (heptet, J = 7 Hz, 1 H), 3.63 (s, 3 H), 4.10 (pentet, J = 8 Hz, 1 H), 5.02 (s, 2 H), 7.47 (s, 1 H), 7.81 (d, J = 8 Hz, 1 H). Mass spectrum: $(M + H)^+$ = 287.

E. N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)valine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 5D provided the desired compound.

F. (2S,3S,5S)-5-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with the resultant compound of Example 5E provided, after silica gel chromatography using 2% methanol in chloroform, 110 mg (58%) of the desired compound (R_f 0.44, 10% methanol in chloroform), mp. 142-145°C. Mass spectrum: $(M + H)^+$ = 708.

Example 6

(2S,3S,5S)-2-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)valinyl)amino)-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with the resultant compound of Example 5E and replacing (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane with (2S,3S,5S)-2-amino-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane provided, after silica gel chromatography using 2% methanol in chloroform, 105 mg (55%) of the desired compound (R_f 0.33, 10% methanol in chloroform), mp. 172-174°C. Mass spectrum: $(M + H)^+ = 708$.

Example 7

A. N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)alanine Methyl Ester.

A solution of 1.12 g (5.56 mmol) of 4-nitrophenyl chloroformate in 20 ml of CH_2Cl_2 was cooled to 0°C and treated sequentially with 0.8 g (5.1 mmol) of 4-(hydroxymethyl)-2-isopropylthiazole and 0.6 ml (5.6 mmol) of 4-methylmorpholine. The resulting solution was stirred at 0°C for 1 h, diluted with CH_2Cl_2, washed with three portions of aqueous $NaHCO_3$, dried over Na_2SO_4, and concentrated in vacuo to give crude (4-(hydroxymethyl)-2-isopropylthiazolyl)methyl 4-nitrophenyl carbonate. A portion (0.53 g, 1.65 mmol) of the residue was taken up in 20 ml of chloroform, treated with 0.23 g (1.67 mmol) of L-alanine methyl ester hydrochloride and 0.36 ml (3.3 mmol) of 4-methylmorpholine, and heated at reflux for 16 h. After being allowed to cool, the solven was removed in vacuo, and the residue was purified by silica gel chromatography using 2% methanol in chloroform to provide 0.45 g (94%) of the desired compound, R_f 0.43 (5% methanol in CH_2Cl_2). ^1H NMR (DMSO-d_6) δ 1.26 (d, J = 8 Hz, 3 H), 1.32 (d, J = 7 Hz, 6 H), 3.27 (heptet, J = 7 Hz, 1 H), 3.63 (s, 3 H), 4.10 (p, J = 8 Hz, 1 H), 5.02 (s, 2 H), 7.47 (s, 1 H), 7.81 (d, J = 8 Hz, 1 H). Mass spectrum: $(M + H)^+ = 287$.

B. N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)alanine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 7A provided the desired compound.

C. (2S,3S,5S)-5-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)alaninyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with the resultant compound of Example 7B provided, after silica gel chromatography using 1% methanol in chloroform, 110 mg (69%) of the desired compound (R_f 0.4, 5% methanol in CH_2Cl_2), mp. 59-61°C. Mass spectrum: $(M + H)^+ = 680$. Anal. Calcd for $C_{34}H_{41}N_5O_6S_2 \cdot 0.5H_2O$: C, 59.28; H, 6.15; N, 10.17. Found: C, 59.37; H, 5.96; N, 10.18.

Example 8

A. (5S,1'S)-5-(1-(tert-Butyloxycarbonylamino)-2-phenylethyl)-dihydrofuran-2(3H)-one.

Prepared from commercially available ethyl-3-bromo-propionate by using the procedure of A.E.DeCamp, et al., (*Tetrahedron Lett.* **1991**, *32*, 1867).

B. (5S,1'S)-5-(1-(tert-Butyloxycarbonylamino)-2-phenylethyl)-3-carboethoxy-dihydrofuran-2(3H)-one.

Lithium diisopropylamide (LDA) was prepared by dropwise addition of 16.5 ml (41.2 mmol) of 2.5 M n-BuLi to a solution of 5.8 ml (41.2 mmol) of diisopropyl amine in 30 ml of dry tetrahydrofuran at -78°C. The LDA solution was stirred for 30 min at -78°C and 6.0 g (19.6 mmol) of the resultant compound of Example 8A in 30 ml of dry tetrahydrofuran was added dropwise. The reaction mixture was stirred for 30 min at -78°C and 4.7 ml (49.1 mmol) of

ethyl chloroformate was then added. After being stirred at -78°C for 5 h, the reaction was quenched with saturated aqueous NH_4Cl, extracted with three 60 ml portions of dichloromethane. The combined organic layers were dried over Na_2SO_4, concentrated in vacuo and the residue was purified by silica gel chromatography using 25% ethyl acetate in hexane to provide 4.73 g (64%) of the desired compound as a white solid. Mass spectrum: $(M+H)^+ = 378$.

C. (5S,1'S)-5-(1-(tert-Butyloxycarbonylamino)-2-phenylethyl)-3-carboethoxy-3-((5-thiazolyl)methyl)dihydrofuran-2(3H)-one.

Sodium metal (536 mg, 23.3 mmol) was dissolved in 10 ml of absolute ethanol. A solution of 4.0 g (10.6 mmol) of the resultant compound of Example 8B in 50 ml of absolute ethanol was added dropwise. The mixture was stirred at ambient temperature for 20 min and 5-chloromethylthiazole hydrochloride was then added. After being stirred at ambient temperature for 60 h, the reaction was cooled in an ice bath, neutralized with 10% citric acid to pH ~6 and extracted with four 50 ml portions of dichloromethane. The combined organic layers were dried over Na_2SO_4, concentrated in vacuo and the residue was purified by silica gel chromatography using 10% methanol in dichloromethane to provide 3.88 g (78%) of the desired compound as a white foamy solid. Mass spectrum: $(M+H)^+ = 475$.

D. (3S,5S,1'S)-5-(1-(tert-Butyloxycarbonylamino)-2-phenylethyl)-3-((5-thiazolyl)methyl)dihydrofuran-2(3H)-one.

A solution of 3.88 g (8.18 mmol) of the resultant compound of Example 8C in 65 ml of dimethoxyethane was treated with 32.7 ml (32.7 mmol) of 1 M aqueous lithium hydroxide. After being stirred at ambient temperature for 4 h, the bulk of the 1,2-dimethoxyethane was removed in vacuo. The remaining mixture was treated with 10% citric acid to pH 4~5 and extracted with four 50 ml portions of dichloromethane. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo to give the crude acid. The acid was dissolved in 50 ml of toluene, heated at reflux for 15 h. The solvent was

removed in vacuo, and the residue was separated by silica gel chromatography using 50% ethyl acetate in hexane to provide 0.86 g (26%) of 3R isomer and 1.58 g (48%) of the desired compound as a white solid. ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 9H), 1.84 (m, 1H), 2.21 (ddd, 1H), 2.82-2.99 (m, 3H), 3.07 (dd, 1H), 3.43 (dd, 1H), 3.97 (br q, 1H), 4.36 (ddd, 1H), 4.55 (br d, 1H), 7.21-7.33 (m, 5H), 7.63 (s, 1H), 8.69 (s, 1H). Mass spectrum: $(M+H)^+$ = 403.

E. (2S,4S,5S)-4-(*tert*-Butyldimethylsilyloxy)-5-(tert-butyloxycarbonylamino)-6-phenyl-2-((5-thiazolyl)-methyl)hexanoic acid.

A solution of 1.50 g (3.73 mmol) of the resultant compound of Example 8D in 80 ml of a 2:1 mixture of 1,2-dimethoxyethane and water was treated with 14.9 ml (14.9 mmol) of 1 M aqueous lithium hydroxide. After being stirred at ambient temperature for 1.5 h, the bulk of the 1,2-dimethoxyethane was removed in vacuo. The remaining mixture was treated with 10% citric acid to pH 4~5 and extracted with four 50 ml portions of dichloromethane. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo to give 1.48 g of the crude hydroxy acid. This hydroxy acid was dissolved in 14 ml of dry DMF and 2.64 g (17.5 mmol) of *tert*-butyldimethylsilyl chloride and 2.23 g (32.8 mmol) of imidazole were added. After being stirred at ambient temperature for 18 h, 28 ml of methanol was added to the mixture. Stirring was continued for 4 h and the solvents were then removed in vacuo. The residue was treated with 10% citric acid to pH 4~5 and extracted with four 50 ml portions of dichloromethane. The combined organic layers were dried over Na_2SO_4, concentrated in vacuo and the residue was purified by silica gel chromatography using 10% methanol in dichloromethane to provide 1.70 g (85%) of the desired compound as a white foamy solid. Mass spectrum: $(M+H)^+$ = 529.

Anal. Calcd for $C_{27}H_{42}N_2O_5SSi \cdot 0.5H_2O$: C, 59.64; H, 7.97; N, 5.15; Found: C, 59.71; H, 7.83; N, 5.31.

F. (2S,3S,5S)-5-((((Benzyl)oxy)carbonyl)amino)-3-(*tert*-butyldimethylsilyloxy)-2-(tert-butyloxycarbonylamino)-1-phenyl-6-(5-thiazolyl)hexane.

A solution of 500.0 mg (0.935 mmol) of the resultant compound of Example 8E, 402 µl (1.87 mmol) of diphenyl-phosphoryl azide and 326 µl (2.38 mmol) of triethylamine in 5 ml of dioxane was heated at 70°C for 1 h. Benzyl alcohol (483 µl, 4.67 mmol) was subsequently added. The mixture was stirred at 80°C for 24 h. The solvents were removed in vacuo and the residue was purified by silica gel chromatography using 10% methanol in dichloromethane to provide 598.1 mg (100%) of the desired compound as a white foamy solid. Mass spectrum: $(M+H)^+ = 640$.

G. (2S,3S,5S)-5-((((Benzyl)oxy)carbonyl)amino)-2-(tert-butyloxycarbonylamino)-1-phenyl-6-(5-thiazolyl)-3-hydroxyhexane.

A solution of 570.6 mg (0.892 mmol) of the resultant compound of Example 8F in 25 ml of tetrahydrofuran was treated with 0.89 ml of 1 M solution of tetrabutylammonium fluoride in tetrahydrofuran. After being stirred at ambient temperature for 20 h, the solvent was removed in vacuo and the residue was purified by silica gel chromatography using 10% methanol in dichloromethane to provide 295.6 mg (63%) of the desired compound as a white solid. ^1H NMR ($CDCl_3$) δ 1.39 (s, 9H), 1.54 (m, 2H), 2.87 (m, 2H), 3.08 (m, 2H), 3.69 (m, 2H), 3.96 (m, 1H), 4.77 (br d, 1H), 5.08 (s, 2H), 5.11 (br s, 1H), 7.18-7.36 (m, 10H), 7.53 (s, 1H), 8.67 (s, 1H). Mass spectrum: $(M+H)^+ = 526$.

H. (2S,3S,5S)-2,5-Diamino-1-phenyl-6-(5-thiazolyl)-3-hydroxyhexane.

The resultant compound of Example 8G (201.2 mg, 0.383 mmol) was dissolved in 1 ml of acetic acid saturated with hydrogen bromide and stirred at ambient temperature for 1 h. The solvent was removed in vacuo. The residue was treated with 2 ml of saturated aqueous $NaHCO_3$, extracted with five 5 ml portions of dichloromethane. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo to provide 99.3 mg (89%) of the desired compound as a white solid. Mass spectrum: $(M+H)^+ = 292$.

I. (4S,6S,1'S)-6-(1-Amino-2-phenylethyl)-2-phenyl-4-((5-thiazolyl)methyl)-3-aza-2-bora-1-oxacyclohexane.

A solution of 95.7 mg (0.328 mmol) of the resultant compound of Example 8H and 40.0 mg (0.328 mmol) of phenylboric acid in 5 ml of toluene was heated at reflux and the water azeotropically removed with the aid of a Dean Stark trap until the distillate was clear. The solvent was then removed in vacuo to provided 124.3 mg (100%) of the desired compound as a resin. Mass spectrum: $(M+H)^+ = 378$.

J. (2S,3S,5S)-5-Amino-1-phenyl-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-6-(5-thiazolyl)-3-hydroxyhexane.

A solution of 100.0 mg (0.265 mmol) of the resultant compound of Example 8I and 74.0 mg (0.265 mmol) of ((5-thiazolyl)methyl)-(4-nitrophenyl)carbonate in 5 ml of tetrahydrofuran was stirred at ambient temperature for 24 h. The solvent was then removed in vacuo. The residue was dissolved in 20 ml of dichloromethane, washed with three 5 ml portions of 0.5N NaOH and two 5 ml portions of water. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel chromatography using 2% methanol and 2% isopropylamine in chloroform to provide 22.8 mg (20%) of the desired compound as a white solid. Mass spectrum: $(M+H)^+ = 433$.

K. (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-1-phenyl-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-6-(5-thiazolyl)-3-hydroxyhexane.

Using the procedure of Example 1U but replacing (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane with the resultant compound of Example 8J provided 16.7 mg (47%) of the desired compound as a white solid. ^1H NMR ($CDCl_3$) δ 0.90 (d, 3H), 0.94 (d, 3H), 1.38 (d, 6H), 1.63 (m, 2H), 2.32 (m, 1H), 2.85 (m, 2H), 2.97 (s, 3H), 3.04 (m, 2H), 3.31

(m, 1H), 3.68 (m, 1H), 3.77 (m, 1H), 3.96 (m, 1H), 4.16 (m, 1H), 4.39 (s, 2H), 5.22 (m, 4H), 6.40 (br s, 1H), 6.80 (br d, 1H), 7.04 (s, 1H), 7.18-7.28 (m, 5H), 7.55 (s, 1H), 7.83 (s, 1H), 8.58 (s, 1H), 8.80 (s, 1H). Mass spectrum: $(M+H)^+$ = 728.

Example 9

A. 4-(Chloromethyl)-2-(dimethylamino)thiazole.

A mixture of 15 g (144 mmol) of N,N-dimethylthiourea and excess $MgSO_4$ in 350 ml of acetone was heated to reflux and treated dropwise with a solution of 18.3 g (144 mmol) of 1,3-dichloroacetone in 35 ml of acetone. The resulting mixture was heated at reflux for 1.5 h, allowed to cool, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography using 20% ethyl acetate in hexane to provide 14.0 g (70%) of the desired compound.

B. 2-(N,N-Dimethylamino)-4-(hydroxymethyl)thiazole.

A solution of 5.186 g (29 mmol) of 4-(chloromethyl)-2-(dimethylamino)thiazole in 100 ml of 1:1 THF/H_2O was cooled to 0°C and treated dropwise with a solution of 5.73 g (29 mmol) of silver tetrafluoroborate in 50 ml of 1:1 THF/H_2O. After being stirred for 1 h, the mixture was filtered, the solid mass was washed with ethyl acetate, and the combined filtrates were concentrated in vacuo. The black residue was purified by silica gel chromatography to provide 0.80 g (17%) of the desired compound (R_f 0.24, 6% methanol in chloroform) as an oil. ^1H NMR ($CDCl_3$) δ 2.67 (br, 1 H), 3.09 (s, 6 H), 4.54 (s, 2 H), 6.35 (s, 1 H). Mass spectrum: $(M + H)^+$ = 159.

C. N-((2-(N,N-Diethylamino)-4-thiazolyl)methoxycarbonyl)valine Methyl Ester.

A solution of 505 mg (3.19 mmol) of 2-(N,N-dimethylamino)-4-(hydroxymethyl)thiazole, 3.19 mmol of α-isocyanato-L-valine methyl ester, and 100 mg of 4-dimethylaminopyridine in 30 ml of dichloromethane was heated at reflux for 3 h. The resulting solution was allowed to cool, diluted with

dichloromethane, washed sequentially with 10% citric acid, aqueous Na_2CO_3, and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel chromatography using 2% methanol in chloroform to provide 0.95 g (95%) of the desired compound, R_f 0.42 (4% methanol in chloroform). ^1H NMR ($CDCl_3$) δ 0.84 (d, J = 7 Hz, 3 H), 0.93 (d, J = 7 Hz, 3 H), 2.12 (m, 1 H), 3.11 (s, 6 H), 3.73 (s, 3 H), 4.24 (dd, J = 8, 4 Hz, 1 H), 4.99 (s, 2 H), 5.26 (br d, 1 H), 6.49 (s, 1 H). Mass spectrum: $(M + H)^+ = 316$.

D. N-((2-(N,N-Dimethylamino)-4-thiazolyl)methoxycarbonyl)valine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 9C provided the desired compound. Mass spectrum: $(M + H)^+ = 302$.

E. (2S,3S,5S)-5-(N-(N-((2-(N,N-Dimethylamino)-4-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with the resultant compound of Example 9D provided, after silica gel chromatography using 2% methanol in chloroform, 100 mg of the desired compound (R_f 0.49, 10% methanol in chloroform), mp. 162-165°C. Mass spectrum: $(M + H)^+ = 709$.

Example 10

(2S,3S,5S)-2-(N-(N-((2-(N,N-Dimethylamino)-4-thiazolyl)methoxycarbonyl)valinyl)amino)-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with the resultant compound of Example 9D and replacing (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane with (2S,3S,5S)-2-amino-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-

3-hydroxyhexane provided, after silica gel chromatography using 2% methanol in chloroform, 25 mg (10%) of the desired compound (R_f 0.49, 10% methanol in chloroform), mp. 157-159°C. Mass spectrum: $(M + H)^+ = 709$.

Example 11

A. 4-((Amino)thiocarbonyl)morpholine.

A solution of 3.35 g (18.8 mmol) of thiocarbonyl diimidazole in 100 ml of THF was treated with 0.82 ml (9.4 mmol) of morpholine. After being stirred at ambient temperature for 3.5 h, an additional 0.82 ml portion of morpholine was added, and stirring was continued. After 6 h, the solution was treated with excess concentrated aqueous ammonia, and stirred overnight. The resulting solution was concentrated in vacuo, taken up in chloroform, separated from the aqueous phase, dried over Na_2SO_4, and concentrated. Purification of the residue by silica gel chromatography using ethyl acetate provided 1.85 g (76%) of the desired compound, R_f 0.17 (10% methanol in chloroform), as a white solid. ^1H NMR ($CDCl_3$) δ 3.76 (m, 4 H), 3.83 (m, 4 H), 5.75 (br, 2 H). Mass spectrum: $(M + H)^+ = 147$.

B. Ethyl 2-(4-Morpholinyl)thiazole-4-carboxylate.

A mixture of 1.85 g (12.7 mmol) of 4-((amino)thiocarbonyl)morpholine, 1.59 ml (12.7 mmol) of ethyl bromopyruvate, and excess $MgSO_4$ in 50 ml of acetone was heated at reflux for 2 h. The resulting mixture was allowed to cool, filtered, and concentrated in vacuo. The residue was taken up in chloroform, washed with aqueous $NaHCO_3$, dried over Na_2SO_4, and concentrated. Silica gel chromatography using 1% methanol in chloroform provided 1.7 g (55%) of the desired compound, R_f 0.70 (ethyl acetate). Mass spectrum: $(M + H)^+ = 243$.

C. 2-(4-Morpholinyl)-4-(hydroxymethyl)thiazole.

A solution of 7.0 ml (7.0 mmol) of lithium aluminum hydride in toluene was diluted with 10 ml of THF, cooled to 0°C, and treated with a solution of 1.7 g (7.0 mmol) of ethyl 2-(4-morpholinyl)thiazole-4-carboxylate in 25 ml of THF.

The resulting solution was stirred for 1 h, quenched cautiously with aqueous Rochelle's salts, diluted with chloroform, filtered, dired over Na_2SO_4, and concentrated in vacuo. Silica gel chromatography using 2-4% methanol in chloroform provided 856 mg (61%) of the desired compound, R_f 0.16 (4% methanol in chloroform). ^1H NMR ($CDCl_3$) δ 2.44 (br, 1 H), 3.46 (t, J = 5 Hz, 4 H), 3.81 (t, J = 5 Hz, 1 H), 4.55 (br s, 2 H), 6.45 (s, 1 H). Mass spectrum: $(M + H)^+ = 200$.

D. N-((2-(4-Morpholinyl)-4-thiazolyl)methoxycarbonyl)valine Methyl Ester.

Using the procedure of Example 9C but replacing 2-(N,N-dimethylamino)-4-(hydroxymethyl)thiazole with 2-(4-morpholinyl)-4-(hydroxymethyl)thiazole provided, after silica gel chromatography using 1% methanol in chloroform, the desired compound, R_f 0.54 (4% methanol in chloroform), in 65% yield. ^1H NMR ($CDCl_3$) δ 0.97 (d, J = 7 Hz, 3 H), 1.00 (d, J = 7 Hz, 3 H), 2.25 (m, 1 H), 3.50 (dd, J = 5, 4 Hz, 2 H), 3.76 (s, 3 H), 3.84 (dd, J = 5, 4 Hz, 2 H), 4.67 (dd, J = 9, 5 Hz, 1 H), 7.63 (br d, 1 H), 8.02 (s, 1 H).

E. N-((2-(4-Morpholinyl)-4-thiazolyl)methoxycarbonyl)valine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 11D provided the desired compound.

F. (2S,3S,5S)-5-(N-(N-((2-(4-Morpholinyl)-4-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with the resultant compound of Example 11E provided, after silica gel chromatography using 2% methanol in chloroform, 201 mg (92%) of the desired compound (R_f 0.19, 4% methanol in chloroform), mp. 169-170°C. Mass spectrum: $(M + H)^+ = 751$.

Example 12

(2S,3S,5S)-2-(N-(N-((2-(4-Morpholinyl)-4-thiazolyl)-methoxycarbonyl)valinyl)amino)-5-(N-((5-thiazolyl)-methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with the resultant compound of Example 11E and replacing (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane with (2S,3S,5S)-2-amino-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane provided, after silica gel chromatography using 2% methanol in chloroform, 196 mg (90%) of the desired compound (R_f 0.19, 4% methanol in chloroform), mp. 146-148°C. Mass spectrum: $(M + H)^+ = 751$.

Example 13

A. 1-((Amino)thiocarbonyl)pyrrolidine.

Using the procedure of Example 11A but replacing morpholine with pyrrolidine, and stirring the solution for six days after addition of aqueous ammonia provided the desired compound. ^1H NMR ($CDCl_3$) δ 1.97 (m, 2 H), 2.11 (m, 2 H), 3.38 (br t, 2 H), 3.85 (br t, 2 H), 5.56 (br, 2 H). Mass spectrum: $(M + H)^+ = 131$.

B. Ethyl 2-(1-Pyrrolidinyl)thiazole-4-carboxylate.

Using the procedure of Example 11B but replacing 4-((amino)thiocarbonyl)morpholine with 1-((amino)thiocarbonyl)pyrrolidine provided the desired compound. ^1H NMR ($CDCl_3$) δ 1.37 (t, J = 7 Hz, 3 H), 2.04 (m, 4 H), 3.51 (m, 4 H), 4.35 (q, J = 7 Hz, 2 H), 7.37 (s, 1 H). Mass spectrum: $(M + H)^+ = 227$.

C. 2-(1-Pyrrolidinyl)-4-(hydroxymethyl)thiazole.

Using the procedure of Example 11C but replacing ethyl 2-(4-morpholinyl)thiazole-4-carboxylate with ethyl 2-(1-pyrrolidinyl)thiazole-4-

carboxylate provided, after silica gel chromatography using 2 - 4% methanol in chloroform, the desired compound (R_f 0.26, 4% methanol in chloroform) in 53% yield. ^1H NMR ($CDCl_3$) δ 2.04 (m, 4 H), 2.75 (br, 1 H), 3.45 (m, 4 H), 4.56 (s, 2 H), 6.32 (s, 1 H). Mass spectrum: $(M + H)^+ = 185$.

D. N-((2-(1-Pyrrolidinyl)-4-thiazolyl)methoxycarbonyl)valine Methyl Ester.

Using the procedure of Example 9C but replacing 2-(N,N-dimethylamino)-4-(hydroxymethyl)thiazole with 2-(1-pyrrolidinyl)-4-(hydroxymethyl)thiazole provided, after silica gel chromatography using 1.5% methanol in chloroform, the desired compound (R_f 0.34). ^1H NMR ($CDCl_3$) δ 0.89 (d, J = 7 Hz, 6 H), 2.04 (m, 4 H), 2.14 (m, 1 H), 3.46 (m, 4 H), 3.74 (s, 3 H), 4.30 (dd, J = 9, 4 Hz, 1 H), 5.01 (s, 2 H), 5.33 (br d, 1 H), 6.44 (s, 1 H). Mass spectrum: $(M + H)^+ = 342$.

E. N-((2-(1-Pyrrolidinyl)-4-thiazolyl)methoxycarbonyl)valine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 13D provided the desired compound.

F. (2S,3S,5S)-5-(N-(N-((2-(1-Pyrrolidinyl)-4-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with the resultant compound of Example 13E provided, after silica gel chromatography using 1 - 3% methanol in chloroform, 120 mg (53%) of the desired compound, mp. 146-148°C. Mass spectrum: $(M + H)^+ = 735$.

Example 14

(2S,3S,5S)-2-(N-(N-((2-(1-Pyrrolidinyl)-4-thiazolyl)-methoxycarbonyl)valinyl)amino)-5-(N-((5-thiazolyl)-methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with the resultant compound of Example 13E and replacing (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane with (2S,3S,5S)-2-amino-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane provided, after silica gel chromatography using 2% methanol in chloroform, 89 mg (39%) of the desired compound (R_f 0.16, 4% methanol in chloroform), mp. 165-167°C. Mass spectrum: $(M + H)^+ = 735$.

Example 15

A. 2-Isopropyl-4-(((N-cyclopropyl)amino)methyl)thiazole.

A solution of 1.8 g (10.2 mmol) of 4-(chloromethyl)-2-isopropylthiazole hydrochloride in 10 ml of chloroform was added dropwise with stirring to 10 ml of cyclopropylamine. The resulting solution was stirred at ambient temperature for 16 h, concentrated in vacuo, and purified by silica gel chromatography using 5% methanol in chloroform to provide 0.39 g (19%) of the desired compound. ^1H NMR (DMSO-d_6) δ 0.24 (m, 2 H), 0.35 (m, 2H),1.30 (d, J = 7 Hz, 6 H), 2.10 (tt, J = 12, 3 Hz, 1 H), 3.23 (heptet, J = 7 Hz, 1 H), 3.77 (s, 2 H), 7.21 (s, 1 H). Mass spectrum: $(M + H)^+ = 197$.

B. N-((N-Cyclopropyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-alanine Methyl Ester.

Using the procedure of Example 1S, but replacing N-(((4-nitrophenyl)-oxy)carbonyl)-L-valine methyl ester with N-(((4-nitrophenyl)oxy)carbonyl)-L-alanine methyl ester and replacing 2-isopropyl-4-(((N-methyl)amino)methyl)-thiazole with the resultant compound of Example 15A provided, after silica gel chromatography using 1% methanol in chloroform, the desired compound (R_f

0.54, 5% methanol in chloroform) in 56% yield. ^{1}H NMR (DMSO-d_6) δ 0.70 (m, 2 H), 0.80 (m, 2 H), 1.30 (d, J = 7 Hz, 6 H), 1.34 (d, J = 7 Hz, 3 H), 2.57 (m, 1 H), 3.22 (heptet, J = 7 Hz, 1 H), 3.62 (s, 3 H), 4.23 (pentet, J = 7 Hz, 1 H), 4.44 (AA', 2 H), 6.54 (d, J = 7 Hz, 1 H), 7.05 (s, 1 H). Mass spectrum: $(M + H)^+ = 326$.

C. N-((N-Cyclopropyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-alanine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 15B provided the desired compound.

D. (2S,3S,5S)-5-(N-(N-((N-Cyclopropyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)alaninyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with the resultant compound of Example 15C provided, after silica gel chromatography using 1% methanol in chloroform, 74 mg (40%) of the desired compound (R_f 0.25, 5% methanol in chloroform), mp. 65-67°C. Mass spectrum: $(M + H)^+ = 719$. Anal. Calcd for $C_{37}H_{46}N_6O_5S_2 \cdot 0.5H_2O$: C, 61.05; H, 6.51; N, 11.54. Found: C, 61.08; H, 6.32; N, 11.44.

Example 16

A. 2-Isopropylthiazole-4-carboxaldehyde.

A solution of ethyl 2-isopropyl-4-thiazole carboxylate (1 mmol) in 50 ml of dry dichloromethane was cooled to -78°C under N_2 atmosphere and treated dropwise with 1.2 mmol of diisobutylaluminum hydride (1.5 M in toluene). The resulting solution was stirred for 0.5 h, quenched with aqueous Rochelle salts, extracted with dichloromethane, dried over Na_2SO_4, and concentrated in vacuo to provide the crude desired compound.

B. 4-(1-Hydroxyethyl)-2-isopropylthiazole.

A solution of the resultant compound of Example 16A (0.5 mmol) in 25 ml of dry THF was cooled to -20°C under Ar atmosphere, treated with 0.5 mmol of methylmagnesium chloride (3.0 M in THF), stirred for 15 min, and quenched with water. The mixture was extracted with ethyl acetate, dried over Na_2SO_4, and concentrated in vacuo to provide the crude desired compound.

C. N-(1-(2-Isopropyl-4-thiazolyl)ethoxycarbonyl)valine Methyl Ester.

Using the procedure of Example 5D but replacing 4-(hydroxymethyl)-2-isopropylthiazole with 4-(1-hydroxyethyl)-2-isopropylthiazole provided the desired compound.

D. N-(1-(2-Isopropyl-4-thiazolyl)ethoxycarbonyl)valine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 16C provided the desired compound.

E. (2S,3S,5S)-5-(N-(N-(1-(2-Isopropyl-4-thiazolyl)ethoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with the resultant compound of Example 16D provided the desired compound.

Example 17

A. N-((N-Cyclopropyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine Methyl Ester.

Using the procedure of Example 1S, but replacing 2-isopropyl-4-(((N-methyl)amino)methyl)thiazole with the resultant compound of Example 15A provided, after silica gel chromatography using 1% methanol in chloroform, the desired compound (R_f 0.64, 5% methanol in chloroform) in 91% yield. ^1H NMR

(DMSO-d_6) δ 0.73 (m, 2 H), 0.82 (m, 2 H), 0.90 (d, J = 7 Hz, 6 H), 1.30 (d, J = 7 Hz, 6 H), 2.10 (octet, J = 7 Hz, 1 H), 2.62 (m, 1 H), 3.23 (heptet, J = 7 Hz, 1 H), 3.64 (s, 3 H), 4.10 (dd, J = 9, 6 Hz, 1 H), 4.45 (AA', 2 H), 6.29 (d, J = 9 Hz, 1 H), 7.06 (s, 1 H). Mass spectrum: $(M + H)^+ = 354$..

B. N-((N-Cyclopropyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 17A provided the desired compound.

C. (2S,3S,5S)-5-(N-(N-((N-Cyclopropyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with the resultant compound of Example 17B provided, after silica gel chromatography using 1% methanol in chloroform, 85 mg (48%) of the desired compound (R_f 0.30, 5% methanol in chloroform), mp. 65-66°C. Mass spectrum: $(M + H)^+ = 747$. Anal. Calcd for $C_{39}H_{50}N_6O_5S_2$: C, 62.71; H, 6.75; N, 11.25. Found: C, 62.74; H, 6.61; N, 11.03.

Example 18

A. 4-Chloromethyl-4-hydroxy-2-isopropyloxazoline.

To a solution of isobutyramide (9.876 g, 0.1122 mol) in acetone (130 mL) was added 1,3-dichloroacetone (10.0 g, 0.0748 mol), $NaHCO_3$ (9.429 g, 0.1122 mol), and $MgSO_4$ (18.01 g, 0.1496 mol). The mixture was heated at reflux under argon for 63 hrs, then cooled to room temperature, vacuum filtered, and concentrated in vacuo to a dark brown semi-solid. The residue was purified by SiO_2 flash chromatography using a gradient of EtOAc/CH_2Cl_2 (5%, 10%, 20%, 40%) to obtain the desired product as an orange liquid (6.06 g,

0.0341 mol, 46%): ^{1}H NMR ($CDCl_3$) δ 1.20-1.28 (m, 6H), 2.56-2.72 (m, 1H), 3.70 (s, 2H), 4.18 (d, J=9.6 Hz, 1H), 4.38 (d, J=9.6 Hz, 1H). Mass spectrum: $(M + H)^+$ = 178, 180.

B. 4-Chloromethyl-2-isopropyloxazole .

A solution of 4-chloromethyl-4-hydorxy-2-isopropyloxazoline (4.88 g, 0.0275 mol) in 1,2-dichloroethane (20 mL) was added to a solution of $SOCl_2$ (2.40 mL, 0.0329 mol) in 1,2-dichloroethane (80 mL) at 0° C under argon, and the solution was heated to 70° C. After 15 min at 70° C, the reaction was cooled to room temperature and the solvent removed by rotary evaporation in vacuo. Drying the residue on high vacuum gave the desired compound as a brown semi-solid (4.20 g, 0.0263 mol, 96%): ^{1}H NMR ($CDCl_3$) δ 1.36 (d, J=7.5 Hz, 6H), 3.03-3.18 (m, 1H), 4.50 (s, 2H), 7.56 (s, 1H). Mass spectrum: $(M + H)^+$ =160, 162.

C. 2-Isopropyl-4-(((N-methyl)amino)methyl)oxazole

To 40% aqueous methylamine (100 mL) was added dropwise a suspension of 4-chloromethyl-2-isopropyloxazole (4.20 g, 0.0263 mol) in *p*-dioxane/H_2O (1:1 (v/v), 20 mL) over a 25 min period. After stirring for 45 min at ambient temperature, the volume was reduced to ca. 50 mL by rotary evaporation in vacuo, and NaCl was added. The aqueous was extracted with $CHCl_3$ (4x100 mL), and the combined extract was dried over Na_2SO_4 and concentrated in vacuo. The resulting brown liquid was chromatographed on a 200 g SiO_2 flash column with 2% *i*$PrNH_2/CH_2Cl_2$ followed by a gradient of *i*$PrNH_2$/MeOH/CH_2Cl_2 (0.5:2:97.5, 0.5:4:95.5). Concentration in vacuo of the product-containing fractions afforded the desired compound as a golden oil (2.89 g, 0.0187 mol, 71%): ^{1}H NMR ($CDCl_3$) δ 1.33 (d, J=6.9 Hz, 6H), 2.46 (s, 3H), 2.99-3.14 (m, 1H), 3.64 (s, 2H), 7.42 (s, 1H). Mass spectrum: $(M + H)^+$ = 155, $(M + NH_4)^+$ = 172.

D. N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)-L-valine Methyl Ester.

A solution of N-(((4-nitrophenyl)oxy)carbonyl)-L-valine methyl ester (0.903 g, 0.00305 mol) in anhydrous DMF (6 mL) was added to a solution of 2-isopropyl-4-(((N-methyl)amino)methyl)oxazole (9, 0.470 g, 0.00305 mol) in anhydrous DMF (6 mL) under argon, and the yellow solution was stirred at room temperature for 30 min. Solvent was removed by rotary evaporation in vacuo and the resulting oil dried on high vacuum for 1 hr. The residue was applied to a 150 g SiO_2 flash column and eluted with 20% EtOAc/CH_2Cl_2 and 3% MeOH/CH_2Cl_2. The material obtained after concentration of the product fractions was repurified on a 100 g SiO_2 flash column with a gradient of MeOH/CH_2Cl_2 (1%, 2%, 3%) to obtain the desired compound as an oil (0.515 g, 0.00165 mol, 54 %): ^{1}H NMR ($CDCl_3$) δ 0.97 (dd, J_1=9 Hz, J_2=6.9 Hz, 6H), 1.33 (d, J=6.9 Hz, 6H), 2.11-2.23 (m, 1H), 2.98 (s, 3H), 3.00-3.13 (m, 1H), 3.77 (s, 3H), 4.23-4.36 (m, 2H), 4.36-4.42 (m, 1H), 5.79-5.86 (br d, 1H), 7.46 (s, 1H). Mass spectrum: $(M + H)^+$ = 312.

E. N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)-L-valine.

To a solution of the resultant compound of Example 18D 10 (0.511 g, 0.00164 mol) in *p*-dioxane (10 mL) and H_2O (5 mL) was added LiOH monohydrate (0.103 g, 0.00246 mol). After stirring at room temperature for 1 hr, the *p*-dioxane was removed by rotary evaporation in vacuo, and the remaining aqueous solution was treated with 1N aq HCl (2.46 mL) and extracted with ethyl acetate (4x100 mL). The combined organic extract was washed with saturated brine and dried for 15 mins over Na_2SO_4. Concentration in vacuo followed by CH_2Cl_2 chases (2x) afforded the desired compound as a white solid (0.480 g, 0.00161 mol, 98%): ^{1}H NMR (DMSO-d_6) δ 0.90 (dd, J_1=6.9 Hz, J_2=2.4 Hz, 6H), 1.24 (d, J=6.9 Hz, 6H), 1.99-2.12 (m, 1H), 2.83 (s, 3H), 2.96-3.10 (m, 1H), 3.96 (dd, J_1=8.4 Hz, J_2=6 Hz, 1H), 4.19-4.32 (m, 2H), 6.26 (d, J=8.4 Hz, 1H), 7.80 (s, 1H). Mass spectrum: $(M + H)^+$ = 298

F. (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with N-((N-methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)-L-valine provided, after silica gel chromatography using 3 - 5 - 7% methanol in chloroform, 70 mg, (53%) of the desired compound. ^{1}H NMR (DMSO-d_6) δ 0.74 (d, J=6.3 Hz, 6H), 1.23 (d, J=6.9 Hz, 6H), 1.38-1.51 (m, 2H), 1.80-1.94 (m, 1H), 2.54-2.74 (m, 5H), 2.83 (s, 3H), 2.94-3.09 (m, 1H), 3.53-3.63 (m, 1H), 3.76-3.97 (m, 2H), 4.08-4.35 (m, 3H), 4.63 (d, J=6 Hz, 1H), 5.08-5.19 (m, 2H), 5.90 (d, J=8.7 Hz, 1H), 6.89 (d, J=9 Hz, 1H), 7.07-7.25 (m, 12H), 7.68 (d, J=8.7 Hz, 1H), 7.77 (s, 1H), 7.86 (s, 1H), 9.05 (s, 1H). High resolution mass spectrum: calcd for $C_{37}H_{49}N_6O_6S$: 705.3434. Found: 705.3431 $(M + H)^+$. Anal. Calcd for $C_{37}H_{48}N_6O_6S \cdot 0.5H_2O$: C, 62.25; H, 6.92; N, 11.77. Found: C, 62.35; H, 6.86; N, 11.34.

Example 19

A. Methyl Isocyanide.

A 100 mL 3-neck flask (equipped with septum, stopper, and a short path mini distillation head with cow collector cooled to -78° C) was charged with p-toluenesulfonyl chloride (36.25 g, 0.1901 mol) and quinoline (60 mL). The vigorously stirred solution was heated to 75° C with the system under vacuum (H_2O aspirator with trap cooled to -40° C). Neat N-methylformamide (7.50 g, 0.127 mol) was added via syringe in small portions over 15 mins. The increasingly viscous solution was heated for 10 mins, at which time gas evolution had ceased. Material in the cow collector and in the vacuum trap were combined and vacuum distilled to provide the compound as a colorless liquid (2.06 g, 0.0502 mol, 39%).

B. 5-((Diethoxy)methyl)oxazole.

Prepared according to the procedure of Schöllkopf (*J. Am. Chem. Soc.* 112 (10) 4070 (1990)). To a solution of methyl isocyanide (2.88 g, 0.0702 mol) in THF (50 mL) under argon at -78° C was added dropwise n-butyllithium solution (1.6M in hexanes, 44 mL) over 15 mins. After stirring for an additional 20 mins at -78° C, a solution of ethyl diethoxyacetate (12.62 g, 0.0702 mol) in THF (15 mL) was added dropwise over 20 mins. The bath was allowed to warm to -30° C over the next 2 hrs and the reaction was then stirred at 0° C for 30 mins. The reaction was quenched at 0° C with glacial HOAc (4.22 g, 0.0702 mol) and the solvent was removed by rotary evaporation in vacuo. The golden solid was partitioned with H_2O (45 mL) and EtOAc (200 mL), and the aqueous extracted with EtOAc (2x200 mL). The combined organic was washed with satd aq NaCl, dried over Na_2SO_4, and concentrated in vacuo to a brown oil. Chromatography on a 300 g SiO_2 flash column with a gradient of EtOAc/hexane (10%, 15%, 20%) afforded the desired compound as a colorless liquid (7.46 g, 0.0436 mol, 62%): ^1H NMR ($CDCl_3$) δ 1.25 (t, J=6.9 Hz, 6H), 3.56-3.70 (m, 4H), 5.62 (s, 1H), 7.26 (s, 1H), 7.86 (s, 1H). Mass spectrum: $(M + H)^+ = 172$.

C. 5-Oxazolecarboxaldehyde

A flask was charged with 5-((diethoxy)methyl)oxazole (1.02 g, 0.00596 mol) and cooled to 0° C. A solution of trifluoroacetic acid/CH_2Cl_2 (1:1 (v/v), 6.7 mL) and H_2O (0.39 mL) was added and the solution stirred at 0° C for 10 min. The solvent was removed in vacuo, and the residue was treated with toluene and concentrated. Chromatography on a 100 g SiO_2 flash column with a gradient of EtOAc/hexane (20%, 30%, 40%) afforded the desired compound as a colorless liquid (0.344 g, 0.00354 mol, 59%): ^1H NMR ($CDCl_3$) δ 7.89 (s, 1H), 8.12 (s, 1H), 9.87 (s, 1H). Mass spectrum: $(M + H)^+ = 98$.

D. 5-(Hydroxymethyl)oxazole

A solution of 5-oxazolecarboxaldehyde (0.627 g, 0.00646 mol) in MeOH (10 mL) under argon at 0° C was treated with $NaBH_4$ (0.247 g, 0.00646 mol). After 5 mins the reaction was quenched with acetone and the solvent removed by rotary evaporation in vacuo. Chromatography on a 100 g SiO_2 flash column with a gradient of MeOH/CH_2Cl_2 (5%, 10%) afforded the desired compound as a colorless oil (0.408 g, 0.00412 mol, 64%): ^1H NMR ($CDCl_3$) δ 2.03 (t, J=6.0 Hz, 1H), 4.70 (d, J=6.0 Hz, 2H), 7.04 (s, 1H), 7.87 (s, 1H). MS (Cl/NH_3) m/e 117 (m+NH_4), 100 (m+H).

E. ((5-Oxazolyl)methyl)-(4-nitrophenyl)carbonate.

A solution of 5-(hydroxymethyl)oxazole (1.31 g, 0.0132 mol) in CH_2Cl_2 (70 mL) under argon at 0° C was treated with triethylamine (1.90 mL, 0.0139 mol) and 4-nitrophenyl chloroformate (2.75 g, 0.0132 mol). After stirring at 0° C for 2.5 hrs, solvent was removed by rotary evaporation in vacuo and the yellow solid was dried on vacuum pump to provide the crude desired compound.

F. (2S,3S,5S)-2-Amino-5-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

A solution of crude ((5-oxazolyl)methyl)-(4-nitrophenyl)carbonate (made from 0.0132 mol 5-(hydroxymethyl)oxazole) in THF (110 mL) under argon was treated with a solution of (2S,3S,5S)-2,5-diamino-1,6-diphenyl-3-hydroxyhexane (3.76 g, 0.0132 mol) in THF (20 mL), and the reaction stirred at room temperature for 16 hrs. Solvent was removed by rotary evaporation in vacuo and the yellow foam dried on a vacuum pump. Chromatography on a 200 g SiO_2 flash column with 5% MeOH/CH_2Cl_2, 2% *i*PrNH$_2$/CH_2Cl_2, and a gradient of *i*PrNH$_2$/MeOH/CH_2Cl_2 (2:2:96, 2:5:93) afforded a mixture (1.74 g) of the desired compound and (2S,3S,5S)-5-amino-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane. The mixture was applied to a 150 g SiO_2 flash column (deactivated with 2% *i*PrNH$_2$/CH_2Cl_2) and eluted with 2% *i*PrNH$_2$/CH_2Cl_2 to afford the desired

compound as a gummy light yellow solid (0.382 g, 0.933 mmol, 7%): ^{1}H NMR (DMSO-d_6) δ 1.16-1.30 (m, 1H), 1.36-1.47 (m, 1H), 2.56-2.66 (m, 2H), 2.75-2.85 (m, 1H), 2.89-3.01 (m, 1H), 3.53-3.71 (m, 3H), 4.97 (d, J=2.4 Hz, 2H), 7.01 (d, J=9 Hz, 1H), 7.11-7.32 (m, 14H), 8.36 (s, 1H). Mass spectrum: $(M + H)^+ = 410$.

G. (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl)-methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane with (2S,3S,5S)-5-amino-2-(N-((5-oxazolyl)-methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane and replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with N-((N-methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)-L-valine provided, after silica gel chromatography using a gradient of 1% - 4% methanol in dichloromethane, 145 mg (80%) of the desired compound. ^{1}H NMR ($CDCl_3$) δ 0.74 (d, J=6.9 Hz, 6H), 1.23 (d, J=6.9 Hz, 6H), 1.39-1.50 (m, 2H), 1.80-1.94 (m, 1H), 2.56-2.74 (m, 4H), 2.83 (s, 3H), 2.94-3.09 (m, 1H), 3.52-3.62 (m, 1H), 3.72-3.84 (m, 1H), 3.88-3.92 (m, 1H), 4.08-4.35 (m, 3H), 4.62 (d, J=6Hz, 1H), 4.94 (s, 2H), 5.91 (d, J=8.4 Hz, 1H), 6.89 (d, J=9 Hz, 1H), 7.06-7.26 (m, 11H), 7.69 (d, J=9 Hz, 1H), 7.77 (s, 1H), 8.35 (s, 1H). Mass spectrum: $(M + NH_4)^+ = 706$; $(M + H)^+ = 689$. Anal. Calcd for $C_{37}H_{48}N_6O_7 \cdot 0.5\ H_2O$: C, 63.68; H, 7.08; N, 12.04. Found: C, 63.50; H, 7.13; N, 11.60.

Example 20

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane with (2S,3S,5S)-5-amino-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-

3-hydroxyhexane provided, after silica gel chromatography using 1% methanol in chloroform, 88 mg (55%) of the desired compound (R_f 0.4, 5% methanol in chloroform), mp. 59-61°C. Mass spectrum: $(M + H)^+ = 705$. Anal. Calcd for $C_{37}H_{48}N_6O_6S \cdot 0.5H_2O$: C, 62.25; H, 6.92; N, 11.77. Found: C, 62.23; H, 6.55; N, 11.57.

Example 21

A. Methyl 4-isopropyl-2-thiazolecarboxylate.

A mixture of 2.11 g (12.8 mmol) of 1-bromo-3-methylbutan-2-one (Gaudry and Marquet, Tetrahedron, 26, 5661 (1970)), 1.0 g (12.8 mmol) of ethyl thiooxamate, and 1.70 g (14 mmol) of $MgSO_4$ in 50 ml of acetone was heated at reflux for 3 h. After being allowed to cool, the mixture was filtered, concentrated in vacuo, and purified by silica gel chromatography using chloroform to provide 0.29 g (11%) of the desired compound (R_f 0.9, 4% methanol in chloroform). ^1H NMR (DMSO-d_6) δ 1.27 (d, J = 7 Hz, 6 H), 1.32 (t, J = 7 Hz, 3 H), 3.12 (heptet, J = 7 Hz, 1 H), 4.37 (q, J = 7 Hz, 2 H), 7.73 (s, 1 H). Mass spectrum: $(M + H)^+ = 200$.

B. 2-(Hydroxymethyl)-4-isopropylthiazole.

Using the procedure of Example 5B, but replacing ethyl 2-isopropyl-4-thiazolecarboxylate with methyl 4-isopropyl-2-thiazolecarboxylate provided, after silica gel chromatography using 2% methanol in chloroform, the desired compound (R_f 0.3, 5% methanol in chloroform) in 96% yield.

C. N-((4-Isopropyl-2-thiazolyl)methoxycarbonyl)alanine Methyl Ester.

A solution of 1.4 mmol of α-isocyanato-alanine methyl ester (prepared from L-alanine methyl ester hydrochloride according to the procedure of Example 5C) and 0.22 g (1.4 mmol) of 2-(hydroxymethyl)-4-isopropylthiazole in 10 ml of chloroform was heated at reflux for 3 h. After being allowed to cool, the solvent was removed in vacuo, and the residue was purified by silica gel chromatography using 2% methanol in chloroform to provide 0.23 g (52%) of

the desired compound (R_f 0.54, 5% methanol in dichloromethane). NMR ^1H NMR (DMSO-d_6) δ 0.87 (d, J = 7 Hz, 3 H), 0.88 (d, J = 7 Hz, 3 H), 1.23 (d, J = 7 Hz, 6 H), 2.04 (octet, J = 7 Hz, 1 H), 3.01 (heptet, J = 7 Hz, 1 H), 3.73 (s, 3 H), 3.94 (dd, J = 8, 6 Hz, 1 H), 5.26 (AA', 2 H), 7.28 (s, 1 H), 7.92 (d, J = 8 Hz, 1 H). Mass spectrum: $(M + H)^+ = 158$.

D. N-((4-Isopropyl-2-thiazolyl)methoxycarbonyl)alanine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 21C provided the desired compound.

E. (2S,3S,5S)-5-(N-(N-((4-Isopropyl-2-thiazolyl)methoxycarbonyl)alaninyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with the resultant compound of Example 21D provided, after silica gel chromatography using 1% methanol in chloroform, 123 mg (61%) of the desired compound (R_f 0.4, 5% methanol in chloroform), mp. 62-64°C. Mass spectrum: $(M + H)^+ = 708$.

Example 22

A. N,N-Diethylthiourea

A mixture of 6.24 g (35 mmol) of thiocarbonyl diimidazole and 3.6 ml (35 mmol) of diethylamine in 50 ml of THF was stirred at ambient temperature for 5 h. The resulting solution was treated with 20 ml of 2 M aqueous NH_3 and stirred for 24 h. After removal of the solvent the residue was purified by chromatography on silica gel to provide N,N-diethylthiourea (R_f 0.28, 4% methanol in chloroform).

B. Ethyl 2-(N,N-Diethylamino)thiazole-4-carboxylate.

A solution of 0.972 g (7.36 mmol) of N,N-diethylthiourea and 1.02 ml (8.1 mmol) of ethyl bromopyruvate in 25 ml of acetone was treated with excess solid $MgSO_4$ and heated at reflux for 1 h. The resulting mixture was filtered, and concentrated in vacuo. Silica gel chromatography using $CHCl_3$ provided 2.36 g (38%) of the desired compound as an oil. Mass spectrum: $(M + H)^+ = 229$.

C. 2-(N,N-Diethylamino)-4-(hydroxymethyl)thiazole.

A solution of 3.14 ml of lithium aluminum hydride in toluene was diluted in a dry flask under N_2 atmosphere with 30 ml of THF. The resulting mixture was cooled to 0°C and treated dropwise with a solution of 1.43 g (6.28 mmol) of ethyl 2-(N,N-diethylamino)thiazole-4-carboxylate in 5 ml of THF. After addition, the solution was allowed to warm slowly to ambient temperature, stirred for 1 h, recooled to 0°C, and treated with a small amount of aqueous Rochelle's salt followed by ethyl acetate. After stirring, the slurry was filtered, washed with additional ethyl acetate, and the combined filtrates were concentrated in vacuo. The residue was purified by silica gel chromatography using methanol in chloroform to provide 0.864 g (73%) of the desired compound, R_f 0.17 (4% methanol in chloroform). Mass spectrum: $(M + H)^+ = 187$.

D. N-((2-(N,N-Diethylamino)-4-thiazolyl)methoxycarbonyl)valine Methyl Ester.

A solution of 5.11 mmol of α-isocyanato-valine methyl ester in 10 ml of dichloromethane was treated with 0.864 g (4.65 mmol) of 2-(N,N-diethylamino)-4-(hydroxymethyl)thiazole and 0.46 mmol of 4-dimethylaminopyridine. The resulting solution was stirred at ambient temperature for 16 h, after which it was diluted with 200 ml of chloroform, washed successively with 10% citric acid, aqueous $NaHCO_3$, and saturated brine. After drying over Na_2SO_4, the solvent was removed in vacuo, and the residue was chromatographed on silica gel using 1-2% methanol in chloroform to provide 1.31 g (82%) of the desired compound, R_f 0.51 (4% methanol in chloroform) as an oil. ^1H NMR ($CDCl_3$) δ 0.89 (d, J = 7 Hz, 3 H), 0.96 (d, J = 7 Hz, 3 H), 1.24 (t, J = 7 Hz, 6 H), 2.15 (m, 1

H), 3.51 (q, J = 7 Hz, 4 H), 3.74 (s, 3 H), 4.29 (dd, J = 8, 4 Hz, 1 H), 5.03 (s, 2 H), 5.34 (br d, J = 8 Hz, 1 H), 6.42 (s, 1 H). Mass spectrum: $(M + H)^+ = 344$.

E. N-((2-(N,N-Diethylamino)-4-thiazolyl)methoxycarbonyl)valine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 22D provided the desired compound.

F. (2S,3S,5S)-5-(N-(N-((2-(N,N-Diethylamino)-4-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with the resultant compound of Example 22E provided the desired compound.

Example 23

A. 2-(N,N-Dimethylamino)-4-(((N-methyl)amino)methyl)thiazole.

Using the procedure of Example 1Q but replacing 4-(chloromethyl)-2-isopropylthiazole hydrochloride with 4-(chloromethyl)-2-(dimethylamino)-thiazole dihydrochloride provided, after silica gel chromatography using first 10% methanol in chloroform followed by 4% methanol/2% isopropylamine in chloroform, the desired compound, R_f 0.05 (10 % methanol in chloroform). ^1H NMR ($CDCl_3$) δ 2.46 (s, 3 H), 3.08 (s, 6 H), 3.66 (s, 2 H), 6.30 (s, 1 H). Mass spectrum: $(M + H)^+ = 172$.

B. N-((N-Methyl-N-(((N,N-dimethylamino)-4-thiazolyl)methyl)amino)carbonyl)-L-valine Methyl Ester.

A solution of 741 mg (4.42 mmol) of α-isocyanato-L-valine in in 5 ml of dichloromethane was added to a solution of 720 mg (4.21 mmol) of 2-(N,N-dimethylamino)-4-(((N-methyl)amino)methyl)thiazole in 25 ml of dichloromethane. The resulting solution was stirred at ambient temperature for

16 h, partitioned between chloroform and aqueous $NaHCO_3$, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel chromatography using 2% methanol in chloroform to provide 463 mg (34%) of the desired compound, R_f 0.25 (2% methanol in chloroform). NMR ($CDCl_3$) δ 0.96 (d, J = 7 Hz, 3 H), 0.98 (d, J = 7 Hz, 3 H), 2.13 (m, 1 H), 2.97 (s, 3 H), 3.11 (s, 6 H), 3.71 (s, 3 H), 4.07 (br d, J = 16 Hz, 1 H), 4.34 (dd, J = 9, 5 Hz, 1 H), 4.42 (d, J = 16 Hz, 1 H), 6.29 (s, 1 H), 6.37 (br, 1 H). Mass spectrum: $(M + H)^+ = 329$.

C. N-((N-Methyl-N-(((N,N-dimethylamino)-4-thiazolyl)methyl)amino)carbonyl)-L-valine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 23B provided the desired compound.

D. (2S,3S,5S)-5-(N-(N-((N-Methyl-N-(((N,N-dimethylamino)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with the resultant compound of Example 23C provided, after silica gel chromatography, the desired compound.

Example 24

A. Ethyl 2-Isopropylthiazole-5-carboxylate.

Using the procedure of Example 1J but replacing thioformamide with 2-methylpropane-thioamide provided, after silica gel chromatography using 9:1 ethyl acetate:hexane, the desired compound, R_f 0.8, (5% methanol in chloroform) in 83% yield.

B. 5-(Hydroxymethyl)-2-isopropylthiazole.

Using the procedure of Example 5B, but replacing ethyl 2-isopropyl-4-thiazolecarboxylate with ethyl 2-isopropylthiazole-5-carboxylate provided, after silica gel chromatography using 3% methanol in chloroform, the desired compound, R_f 0.3, (5% methanol in chloroform) in 25% yield.

C. N-((2-Isopropyl-5-thiazolyl)methoxycarbonyl)valine Methyl Ester.

Using the procedure of Example 5D but replacing 4-(hydroxymethyl)-2-isopropylthiazole with 5-(hydroxymethyl)-2-isopropylthiazole provided, after silica gel chromatography using 3% methanol in chloroform, the desired compound, R_f 0.8, (5% methanol in chloroform) in 29% yield. ^1H NMR δ 0.89 (d, J = 7 Hz, 6 H), 0.95 (d, J = 7 Hz, 3 H), 0.97 (d, J = 7 Hz, 3 H), 2.14 (m, 1 H), 3.33 (heptet, J = 7 Hz, 1 H), 3.74 (s, 3 H), 4.30 (dd, J = 9, 5 Hz, 1 H), 5.23 (s, 2 H), 5.25 (br d, 1 H), 7.63 (s, 1 H). Mass spectrum: $(M + H)^+ = 315$.

D. N-((2-Isopropyl-5-thiazolyl)methoxycarbonyl)valine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 24C provided the desired compound.

E. (2S,3S,5S)-5-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with the resultant compound of Example 24D provided the desired compound.

Example 25

A. 2-Methoxythioacetamide.

Using the procedure of Example 1O but replacing isobutyramide with 2-methoxyacetamide provided the desired compound in 52% yield.

B. 4-(Chloromethyl)-2-(methoxymethyl)thiazole hydrochloride.

Using the procedure of Example 1P but replacing 2-methylpropane-thioamide with 2-methoxythioacetamide provided the crude desired compound in 41% yield.

C. 2-(Methoxymethyl)-4-(((N-methyl)amino)methyl)thiazole.

Using the procedure of Example 1Q but replacing 4-(chloromethyl)-2-isopropylthiazole hydrochloride with 4-(chloromethyl)-2-(methoxymethyl)-thiazole hydrochloride provided, after silica gel chromatography using 3% methanol in chloroform, the desired compound, R_f 0.1, (5% methanol in chloroform) in 73% yield.

D. N-((N-Methyl-N-((2-(methoxymethyl)-4-thiazolyl)methyl)amino)carbonyl)-L-valine Methyl Ester.

Using the procedure of Example 1S but replacing 2-isopropyl-4-(((N-methyl)amino)-methyl)thiazole with 2-(methoxymethyl)-4-(((N-methyl)amino)-methyl)thiazole provided, after silica gel chromatography using 3% methanol in chloroform, the desired compound, R_f 0.5, (5% methanol in chloroform) in 23% yield.

E. N-((N-Methyl-N-((2-(methoxymethyl)-4-thiazolyl)methyl)amino)carbonyl)-L-valine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 25D provided the desired compound.

F. (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(methoxymethyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with the resultant compound of Example 25E provided the desired compound.

Example 26

A. 1,1-Diethoxy-4-((3,4,5,6-tetrahydro-2H-pyran-2-yl)oxy)-2-butyne.

A 1 M solution of ethylmagnesium bromide in THF (200 ml, 0.2 mol) was treated with 29 ml (0.2 mol) of a solution of 3,4,5,6-tetrahydro-2-(2-propynyloxy)-2H-pyran in toluene, while maintaining ambient temperature through use of a cool water bath. The resulting solution was stirred for 4 h and treated with 47 ml (.28 mol) of a solution of triethylorthoformate in toluene, while maintaining ambient temperature with a cool water bath. The resulting solution was heated to 85°C for 8 h, allowing the removal of THF by distillation. After being allowed to cool, the resulting solution was poured into 500 ml of ice-water containing 29 g of NH_4OAc, extracted with two portions of ether, dried over K_2CO_3, and concentrated in vacuo. The residue was distilled at ca. 0.5 mm Hg pressure (b.p. 103 - 108°C) to provide 39.5 g (79%) of the desired compound. ^1H NMR ($CDCl_3$) δ 1.24 (t, J = 7 Hz, 6 H), 1.5-1.9 (m, 6 H), 3.5-3.65 (m, 3 H), 3.7-3.9 (m, 3 H), 4.32 (AA', 2 H), 4.81 (m, 1 H), 5.31 (m, 1 H). Mass spectrum: $(M + NH_4)^+ = 260$.

B. 5-(Hydroxymethyl)isoxazole.

A solution of 39.28 g (161 mmol) of the resultant compound of Example 26A and 26 g (376 mmol) of hydroxylamine hydrochloride in 168 ml of ethanol and 34 ml of water was heated at reflux under N_2 atmosphere for 1 h. After being allowed to cool, the resulting solution was concentrated in vacuo to 1/3 the original volume, diluted with 50 ml of water, and extracted with 2 portions, of ether. The combined extracts were concentrated to an oil. The crude product (7.04 g, 44%) was obtained after distillation (79-84°C, 0.5 mm Hg). Silica gel chromatography using 0 -3% methanol in dichloromethane provided 4.9 g of the desired compound contaminated with 5-hydroxypentanal oxime. ^1H NMR

($CDCl_3$) δ 1.95 (br, 1 H), 4.81 (s, 2 H), 6.27 (d, J = 1 Hz, 1 H), 8.23 (d, J = 1 Hz, 1 H). Mass spectrum: $(M + NH_4)^+ = 117$.

C. ((5-Isoxazolyl)methyl)-(4-nitrophenyl)carbonate.

Using the procedure of Example 1L, but replacing 5-(hydroxymethyl)-thiazole with 5-(hydroxymethyl)isoxazole provided, after silica gel chromatography using 8:2 dichloromethane:hexane, the desired compound. ^1H NMR ($CDCl_3$) δ 5.41 (s, 2 H), 6.46 (d, J = 1 Hz, 1 H), 7.40 (m, 2 H), 8.30 (m, 3 H). Mass spectrum: $(M + NH_4)^+ = 282$.

D. (2S,3S,5S)-5-Amino-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

A mixture of 1.54 g (5.41 mmol) of (2S,3S,5S)-2,5-diamino-1,6-diphenyl-3-hydroxyhexane and 0.673 g (5.41 mmol) of phenylboric acid in anhydrous toluene (130 mL) was heated at reflux under argon for 2 hrs with removal of H_2O by a Dean-Stark trap. The resulting yellow solution was allowed to cool and the solvent was removed in vacuo to give an oil which solidified upon standing. The residue was taken up in 90 ml of THF, cooled to -40°C, and treated dropwise under Ar atmosphere over a period of 1 h with 1.11 g (3.78 mmol) of ((5-isoxazolyl)methyl)-(4-nitrophenyl)carbonate in 40 ml of THF. The solution was allowed to warm to -20° C over the next 0.5 hr, then was stirred at 0° C for 2.5 hrs and at room temperature for 1 hr. After removal of the solvent in vacuo, the residue was taken up in ethyl acetate (200 mL), washed sequentially with 5% aqueous K_2CO_3 (4x25 mL) and saturated brine (25 mL), dried over Na_2SO_4 and concentrated in vacuo. Silica gel chromatography of the residue using a gradient of methanol in chloroform (2%, 4%, 6%) afforded a mixture of the desired product and its regioisomer. Purification of the mixture on two consecutive 250 g SiO_2 columns (deactivated with 1% isopropylamine/CH_2Cl_2) with a gradient of isopropylamine/CH_2Cl_2 (0.5%, 1%) afforded the desired compound as a sticky solid (0.730 g, 1.78 mmol, 33%): ^1H NMR (DMSO-d_6) δ 1.17-1.57 (m, 5H), 2.56-2.69 (m, 2H), 2.75-2.86 (m, 1H), 2.89-3.00 (m, 2H),

3.53-3.71 (m, 3H), 5.06 (s, 2H), 6.32 (d, J=2.4 Hz, 1H), 7.11-7.30 (m, 10H), 8.54 (d, J=2.4 Hz, 1H). Mass spectrum: $(M + H)^+ = 410$.

E. (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane with (2S,3S,5S)-5-amino-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane provided, after silica gel chromatography using 1% methanol in chloroform, 120 mg (70%) of the desired compound, R_f 0.3, (5% methanol in chloroform). Mass spectrum: $(M + H)^+ = 705$.

Example 27

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl)-methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane with (2S,3S,5S)-5-amino-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane and replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with N-((N-methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)-L-valine provided, after silica gel chromatography using a gradient of 1 - 4% methanol in dichloromethane, 225 mg (80%) of the desired compound. ^{1}H NMR (DMSO-d_6) δ 0.74 (d, J=6.9 Hz, 6H), 1.23 (d, J=6.9 Hz, 6H), 1.35-1.54 (m, 2H), 1.80-1.95 (m, 1H), 2.55-2.73 (m, 4H), 2.83 (s, 3H), 2.94-3.09 (m, 1H), 3.53-3.63 (m, 1H), 3.73-3.86 (m, 1H), 3.92 (t, J=8.4 Hz, 1H), 4.08-4.34 (m, 3H), 4.65 (d, J=6 Hz, 1H), 5.04 (s, 2H), 5.91 (d, J=9 Hz, 1H), 6.29 (d, J=2.4 Hz, 1H), 7.01 (d, J=9 Hz, 1H), 7.06-7.27 (m, 10H), 7.69 (d, J=9 Hz, 1H), 7.77 (s, 1H), 8.52 (d, J=2.4 Hz, 1H). Mass spectrum: $(M + H)^+ = 689$; $(M + NH_4)^+ = 706$.

Example 28

A. Ethyl 2-Methylthiazole-5-carboxylate.

Using the procedure of Example 1J, but replacing thioformamide with thioacetamide provided the crude desired compound.

B. 5-(Hydroxymethyl)-2-methylthiazole.

Using the procedure of Example 1K, but replacing ethyl thiazole-5-carboxylate with crude ethyl 2-methylthiazole-5-carboxylate provided, after silica gel chromatography using 3% then 5% methanol in chloroform, the desired compound, R_f 0.27, (4% methanol in chloroform) in 78% yield. ^1H NMR ($CDCl_3$) δ 2.32 (br, 1 H), 2.70 (s, 3 H), 4.80 (s, 2 H), 7.46 (s, 1 H). Mass spectrum: $(M + H)^+ = 130$.

C. ((2-Methyl-5-thiazolyl)methyl)-(4-nitrophenyl)carbonate.

Using the procedure of Example 1L, but replacing 5-(hydroxymethyl)-thiazole with 5-(hydroxymethyl)-2-methylthiazole provided, after silica gel chromatography using first 1:5 chloroform:hexane, then 4% methanol in chloroform, the desired compound, R_f 0.46 (20% ethyl acetate in chloroform) in 97% yield.

D. (2S,3S,5S)-5-Amino-2-(N-((2-methyl-5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane and (2S,3S,5S)-2-Amino-5-(N-((2-methyl-5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1M, but replacing ((5-thiazolyl)methyl)-(4-nitrophenyl)carbonate with ((2-methyl-5-thiazolyl)methyl)-(4-nitrophenyl)-carbonate provided, after silica gel chromatography using 4% methanol in chloroform, a mixture of the desired compounds. A second chromatography using 1% - 3% isopropylamine in chloroform provided pure (2S,3S,5S)-5-amino-2-(N-((2-methyl-5-thiazolyl)methoxycarbonyl)-amino)-1,6-diphenyl-3-

hydroxyhexane and (2S,3S,5S)-2-amino-5-(N-((2-methyl-5-thiazolyl)methoxy-carbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

E. (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((2-methyl-5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane with (2S,3S,5S)-5-amino-2-(N-((2-methyl-5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane provided, after silica gel chromatography using 2% methanol in chloroform, 210 mg (84%) of the desired compound, R_f 0.18, (4% methanol in chloroform). Mass spectrum: $(M + H)^+$ =735.

Example 29

A. 5-Methyl-1-((3,4,5,6-tetrahydro-2H-pyran-2-yl)oxy)-2-hexyn-4-one.

The desired compound was prepared from isobutyryl chloride and 3,4,5,6-tetrahydro-2-(2-propynyloxy)-2H-pyran by analogy to the procedure of Tohda, et. al. (Synthesis, 777 (1977)).

B. 5-(Hydroxymethyl)-3-isopropylisoxazole.

Using the procedure of Example 26B but replacing the resultant compound of Example 26A with the resultant compound of Example 29A provided the desired compound.

C. N-((3-Isopropyl-5-isoxazolyl)methoxycarbonyl)valine Methyl Ester.

Using the procedure of Example 5D but replacing 4-(hydroxymethyl)-2-isopropylthiazole with 5-(hydroxymethyl)-3-isopropylisoxazole provided the desired compound.

D. N-((3-Isopropyl-5-isoxazolyl)methoxycarbonyl)valine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 29C provided the desired compound.

E. (2S,3S,5S)-5-(N-(N-((3-Isopropyl-5-isoxazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with the resultant compound of Example 29D provided the desired compound.

Example 30

A. 2-Isopropyl-4-(methanesulfonyloxymethyl)thiazole.

A solution of 1.2 mmol of 4-(hydroxymethyl)-2-isopropylthiazole and 1.3 mmol of diisopropylethylamine in 20 ml of dichloromethane was cooled to -20°C and treated dropwise with 1.3 mmol of methanesulfonyl chloride. The resulting mixture was stirred for 1 h, quenched with aqueous citric acid, separated, dried over Na_2SO_4, and concentrated in vacuo to provide the desired compound.

B. 2-Isopropyl-4-(mercaptomethyl)thiazole.

A mixture of 0.8 mmol of the resultant compound of Example 30A and 1.0 mmol of sodium hydrosulfide hydrate in 20 ml of THF was heated at reflux until analysis by thin layer chromatography indicated consumption of starting material. The resulting mixture was allowed to cool, concentrated in vacuo, partitioned between dichloromethane and water, dried over Na_2SO_4, and concentrated to provide the crude desired compound.

C. N-((2-Isopropyl-4-thiazolyl)thiomethoxycarbonyl)valine Methyl Ester.

Using the procedure of Example 5D, but replacing 4-(hydroxymethyl)-2-isopropylthiazole with the resultant compound of Example 30B provided, after chromatography on silica gel, the desired compound.

D. N-((2-Isopropyl-4-thiazolyl)thiomethoxycarbonyl)valine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 30C provided the desired compound.

E. (2S,3S,5S)-5-(N-(N-((2-Isopropyl-4-thiazolyl)thiomethoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with the resultant compound of Example 30D provided, after purification by silica gel chromatography, the desired compound.

Example 31

A. 2-Isopropylthiazole-4-carboxaldehyde.

A solution of 3.1 g (15.6 mmol) of ethyl 2-isopropylthiazole-4-carboxylate in 50 ml of dichloromethane was cooled under N_2 atmosphere to -78°C and treated dropwise with 15.6 ml (23.4 mmol) of a 1.5 M solution of diisobutylaluminum hydride in toluene over a period of 1.5 h. After being stirred for an additional 0.5 h, the solution was quenched with 5 ml of methanol followed by 15 ml of aqueous Rochelle's salt. The resulting mixture was partitioned between chloroform and aqueous Rochelle's salt, dried over Na_2SO_4, and concentrated to provide 1.37 g (56%) of the crude desired compound, R_f 0.47 (20% ethyl acetate in hexane). ^1H NMR ($CDCl_3$) δ 1.45 (d, J = 7 Hz, 6 H), 3.39 (heptet, J = 7 Hz, 1 H), 8.07 (s, 1 H), 10.00 (s, 1 H). Mass spectrum: $(M + H)^+ = 156$.

B. (E)-Ethyl 3-(2-Isopropyl-4-thiazolyl)propenoate.

A slurry of 60% NaH (18 mmol) in mineral oil was washed with hexane, decante under N_2 atmosphere, and diluted with 25 ml of THF. The resulting mixture was cooled to 0°C, treated portionwise with 3.24 ml (16.4 mmol) of triethylphosphonoacetate. After addition, the solution was stirred for 10 min, treated with 1.37 g (8.84 mmol) of 2-isopropylthiazole-4-carboxaldehyde in 25 ml of THF, allowed to warm to ambient temperature for 25 min, and quenched with 100 ml of saturated aqueous NH_4Cl. The mixture was extracted with three 100 ml portions of ethyl acetate, dried over Na_2SO_4, and concentrated in vacuo. Silica gel chromatography of the residue using 5-10% ethyl acetate in hexane provided 1.61 g (81%) of the desired compound, R_f 0.64 (20% ethyl acetate in hexane). ^1H NMR ($CDCl_3$) δ 1.33 (t, J = 7 Hz, 3 H), 1.42 (d, J = 7 Hz, 6 H), 3.32 (heptet, J = 7 Hz, 1 H), 4.26 (q, J = 7 Hz, 2 H), 6.75 (d, J = 15 Hz, 1 H), 7.29 (s, 1 H), 7.57 (d, J = 15 Hz, 1 H).

C. Methyl 3-(2-Isopropyl-4-thiazolyl)propanoate.

A solution of 225 mg (1 mmol) of (E)-ethyl 3-(2-isopropyl-4-thiazolyl)-propenoate in 10 ml of freshly distilled (from calcium hydride) methanol and 1 ml of dry THF was treated with 49 mg (2 mmol) of magnesium turnings. The mixture was stirred for 20 min, during which the magnesium was consumed. The resulting solution was poured over cold aqueous HCl, basified to pH 8 with $NaHCO_3$, extracted with ethyl acetate, dried over Na_2SO_4, and concentrated. Silica gel chromatography using 10% ethyl acetate in hexane provided a mixture of the desired compound and methyl 3-(2-isopropyl-4-thiazolinyl)propanoate.

D. 3-(2-Isopropyl-4-thiazolyl)propanoic Acid.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 31C provided the desired compound.

E. (2S,3S,5S)-5-(N-(N-(tert-Butyloxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with N-(tert-butyloxy-carbonyl)-L-valine provided, after purification by silica gel chromatography, the desired compound.

F. (2S,3S,5S)-5-(N-(Valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

A solution of 0.1 mmol of the resultant compound of Example 31E was treated with 10 ml of 4N HCl in dioxane, stirred at 0°C for 1 h, concentrated in vacuo, partitioned between chloroform and aqueous $NaHCO_3$, dried over Na_2SO_4, and concentrated to provide the crude desired compound.

G. (2S,3S,5S)-5-(N-(N-(3-(2-Isopropyl-4-thiazolyl)propanoyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with the resultant compound of Example 31D and replacing (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane with the resultant compound of Example 31F provided, after purification by silica gel chromatography, the desired compound.

Example 32

A. Thiazole-5-carboxaldehyde.

Using the procedure of Example 16A but replacing ethyl 2-isopropyl-4-thiazole carboxylate with ethyl thiazole-5-carboxylate provided the desired compound.

B. 5-(1-Hydroxyethyl)thiazole.

Using the procedure of Example 16B but replacing the resultant compound of Example 16A with the resultant compound of Example 32A provided the desired compound.

C. (1-(5-Thiazolyl)ethyl)-(4-nitrophenyl)carbonate.

Using the procedure of Example 1L but replacing 5-(hydroxymethyl)-thiazole with the resultant compound of Example 32B provided the desired compound.

D. (2S,3S,5S)-5-Amino-2-(N-(1-(5-thiazolyl)ethoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 19F but replacing ((5-oxazolyl)methyl)-(4-nitrophenyl)carbonate with (1-(5-thiazolyl)ethyl)-(4-nitrophenyl)carbonate provided, after purification by silica gel chromatography, the desired compound.

E. (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-(1-(5-thiazolyl)ethoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane with the resultant compound of Example 32D provided, after purification by silica gel chromatography, the desired compound.

Example 33

A. ((5-Isothiazolyl)methyl)-(4-nitrophenyl)carbonate.

Using the procedure of Example 1L but replacing 5-(hydroxymethyl)-thiazole with 5-(hydroxymethyl)isothiazole (Bennett, et. al., *J. Chem. Soc.*, 3834 (1965)) provided the desired compound.

B. (2S,3S,5S)-5-Amino-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 19F but replacing ((5-oxazolyl)methyl)-(4-nitrophenyl)carbonate with ((5-isothiazolyl)methyl)-(4-nitrophenyl)carbonate provided, after purification by silica gel chromatography, the desired compound.

C. (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane with the resultant compound of Example 33B provided, after purification by silica gel chromatography, the desired compound.

Example 34

A. (2S,3R,4R,5S)-2,5-Diamino-3,4-dihydroxy-1,6-diphenylhexane.

Using the procedure of Example 1F but replacing the resultant compound of Example 1E with (2S,3R,4R,5S)-2,5-bis-(N-(((benzyl)oxy)-carbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane provided the crude desired compound mixed with benzyl alcohol in 92% yield. Purification of a sample was achieved by silica gel chromatography using 2% isopropylamine in chloroform. ^{1}H NMR ($CDCl_3$) δ 2.71 (dd, J = 13, 9 Hz, 2 H), 2.92 (dd, J = 13, 5 Hz, 2 H), 3.03 (dd, J = 9, 5 Hz, 2 H), 3.68 (s, 2 H), 7.15-7.35 (m, 10 H). Mass spectrum: $(M + H)^+ = 301$.

B. (2S,3R,4R,5S)-2-Amino-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

Using the procedure of Example 1M but replacing (2S,3S,5S)-2,5-diamino-1,6-diphenyl-3-hydroxyhexane with (2S,3R,4R,5S)-2,5-diamino-3,4-

dihydroxy-1,6-diphenylhexane provided, after silica gel chromatography, the desired compound.

C. (2S,3R,4R,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

Using the procedure of Example 1U but replacing (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane with the resultant compound of Example 34B provided, after purification by silica gel chromatography, the desired compound.

Example 35

A. (2S,3S,4S,5S)-2,5-Diamino-3,4-dihydroxy-1,6-diphenylhexane.

Using the procedure of Example 1F but replacing the resultant compound of Example 1E with (2S,3S,4S,5S)-2,5-bis-(N-(((benzyl)oxy)-carbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane provided the desired compound. ^{1}H NMR ($CDCl_3$) δ 2.63 (dd, J = 14, 11 Hz, 2 H), 2.85 (dd, J = 14, 4 Hz, 2 H), 3.60 (dt, J = 11, 4 Hz, 2 H), 3.92 (d, J = 3 Hz, 2 H), 7.2-7.4 (m, 10 H). Mass spectrum: $(M + H)^+ = 301$.

B. (2S,3S,4S,5S)-2-Amino-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

Using the procedure of Example 1M but replacing (2S,3S,5S)-2,5-diamino-1,6-diphenyl-3-hydroxyhexane with (2S,3S,4S,5S)-2,5-diamino-3,4-dihydroxy-1,6-diphenylhexane provided, after silica gel chromatography, the desired compound.

C. (2S,3S,4S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

Using the procedure of Example 1U but replacing (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane with the resultant compound of Example 35B provided, after purification by silica gel chromatography, the desired compound.

Example 36

A. (4S,5S,1'R,2'S)-5-(1-Acetoxy-2-(N-((((benzyl)oxy)carbonyl)amino))-3-phenylpropyl)-4-benzyl-oxazolidin-2-one.

A suspension of 5.02 g (8.80 mmol) of (2S,3R,4R,5S)-2,5-bis-(N-(((benzyl)oxy)carbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane in 400 ml of acetonitrile was treated dropwise with 3 ml (20 mmol) of α-acetoxyisobutyryl bromide. The resulting solution was stirred under N_2 atmosphere at ambient temperature for 2 h, filtered to remove traces of solid starting material, quenched cautiously with 100 ml of aqueous $NaHCO_3$, and concentrated in vacuo to a volume of 100 ml. The resulting mixture was extracted with two 100 ml portions of dichloromethane, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel chromatography using first 10% then 25% ethyl acetate in dichloromethane to provide 3.15 g (71%) of the desired compound as a white foam. ^1H NMR ($CDCl_3$) δ 2.09 (s, 3 H), 2.53 (br t, J = 12 Hz, 1 H), 2.72 (dd, J = 13, 3 Hz, 1 H), 2.83 (dd, J = 14, 8 Hz, 1 H), 2.95 (dd, J = 14, 7 Hz, 1 H), 3.95 (m, 1 H), 4.45 (m, 1 H), 4.8 (m, 2 H), 5.0-5.1 (m, 3 H), 5.29 (dd, J = 9, 3 Hz, 1 H), 7.0-7.4 (m, 10 H). Mass spectrum: $(M + NH_4)^+$ = 520.

B. (2S,3R,4S,5S)-2,5-Diamino-3,4-dihydroxy-1,6-diphenylhexane.

Using the procedure of Example 1F but replacing the resultant compound of Example 1E with (4S,5S,1'R,2'S)-5-(1-acetoxy-2-(N-(benzyl-oxycarbonylamino))-3-phenylpropyl)-4-benzyl-oxazolidin-2-one provided the desired compound mixed with benzyl alcohol. Purification of a small portion by silica gel chromatography using 5% methanol/2% isopropylamine in chloroform provided the pure desired compound., m.p. 115-119°C. ^1H NMR ($CDCl_3$) δ

2.46 (dd, J = 14, 9 Hz, 1 H), 2.61 (dd, J = 14, 11 Hz, 1 H), 3.02 (td, J = 9, 3 Hz, 1 H), 3.19 (dd, J = 14, 4 Hz, 1 H), 3.35-3.4 (m, 2 H), 3.51 (t, J = 9 Hz, 1 H), 3.76 (dd, J = 9, 3 Hz, 1 H), 7.2-7.4 (m, 10 H).

C. (2S,3R,4S,5S)-5-Amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

A solution of 0.133 mmol of (2S,3R,4S,5S)-2,5-diamino-3,4-dihydroxy-1,6-diphenylhexane and 0.147 mmol of ((5-thiazolyl)methyl)-(4-nitrophenyl)-carbonate in 10 ml of tetrahydrofuran was stirred at ambient temperature for 16 h. The resulting solution was diluted with 50 ml of chloroform, washed with several portions of 3N aqueous NaOH, dried over Na_2SO_4, and concentrated in vacuo. Silica gel chromatography of the residue provided the desired compound.

D. (2S,3R,4S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

Using the procedure of Example 1U but replacing (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane with the resultant compound of Example 36C provided, after purification by silica gel chromatography, the desired compound.

Example 37

A. (2S,3R,4S,5S)-2-Amino-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

Using the procedure of Example 1U but replacing (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane with (2S,3R,4S,5S)-2,5-diamino-3,4-dihydroxy-1,6-diphenylhexane provided, after purification by silica gel chromatography, the desired compound.

B. (2S,3R,4S,5S)-2-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

Using the procedure of Example 36C but replacing (2S,3R,4S,5S)-2,5-diamino-3,4-dihydroxy-1,6-diphenylhexane with the resultant compound of Example 37A provided, after purification by silica gel chromatography, the desired compound.

Example 38

A. 5-(Hydroxymethyl)-3-isopropylisothiazole.

The desired compound was prepared from the resultant compound of Example 29A using the procedure of Lucchesini, et. al. (Heterocycles, 29, 97 (1989)).

B. N-((3-Isopropyl-5-isothiazolyl)methoxycarbonyl)valine Methyl Ester.

Using the procedure of Example 5D but replacing 4-(hydroxymethyl)-2-isopropylthiazole with 5-(hydroxymethyl)-3-isopropylisothiazole provided the desired compound.

C. N-((3-Isopropyl-5-isothiazolyl)methoxycarbonyl)valine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 38B provided the desired compound.

D. (2S,3S,5S)-5-(N-(N-((3-Isopropyl-5-isothiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with the resultant compound of Example 38C provided the desired compound.

Example 39

(2S,3S,5S)-2-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-5-(N-((2-methyl-5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane with (2S,3S,5S)-2-amino-5-(N-((2-methyl-5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane provided, after silica gel chromatography using 2% methanol in chloroform, 20 mg (80%) of the desired compound, R_f 0.23, (4% methanol in chloroform). Mass spectrum: $(M + H)^+$ =735

Example 40

Following the procedures of the above Examples, the following compounds can be prepared.

(2S,3R,4S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)alaninyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3R,4S,5S)-5-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3R,4S,5S)-5-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)alaninyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3R,4S,5S)-5-(N-(N-((2-(1-Pyrrolidinyl)-4-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3R,4S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3R,4S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3R,4S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3R,4S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3R,4S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3R,4S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3R,4S,5S)-2-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)alaninyl)amino)-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3R,4S,5S)-2-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)valinyl)amino)-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3R,4S,5S)-2-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)alaninyl)amino)-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3R,4S,5S)-2-(N-(N-((2-(1-Pyrrolidinyl)-4-thiazolyl)methoxycarbonyl)valinyl)amino)-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3R,4S,5S)-2-(N-(N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)valinyl)amino)-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3R,4S,5S)-2-(N-(N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)valinyl)amino)-5-(N-((5-oxazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3R,4S,5S)-2-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-5-(N-((5-oxazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3R,4S,5S)-2-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-5-(N-((5-isoxazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3R,4S,5S)-2-(N-(N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)valinyl)amino)-5-(N-((5-isoxazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3R,4S,5S)-2-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-5-(N-((5-isothiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3R,4R,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)alaninyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3R,4R,5S)-5-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3R,4R,5S)-5-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)alaninyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3R,4R,5S)-5-(N-(N-((2-(1-Pyrrolidinyl)-4-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3R,4R,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3R,4R,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3R,4R,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3R,4R,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3R,4R,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3R,4R,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3S,4S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)alaninyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3S,4S,5S)-5-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3S,4S,5S)-5-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)alaninyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3S,4S,5S)-5-(N-(N-((2-(1-Pyrrolidinyl)-4-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3S,4S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3S,4S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3S,4S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3S,4S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3S,4S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3S,4S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-cyclopentyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-cyclohexyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1,1-dimethyl)ethyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-cyclobutyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-cyclopropyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-ethyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-ethenyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-propenyl)-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-cyclopentenyl)-4-thiazolyl)-methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)-methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-cyclohexenyl)-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((4-cyclopentenyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((4-cyclohexenyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(3-propenyl)-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-propenyl)-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-methyl-1-propenyl)-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-methyl-1-propenyl)-4-thiazolyl)-methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)-amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1,2-dimethyl-1-propenyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)-methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(cyclopentyl)methyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(cyclohexyl)methyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-phenyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-benzyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-phenyl)ethyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-phenyl-1-ethenyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)-methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(4-fluoro)phenyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-chloro)phenyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(3-methoxy)phenyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-thiazolyl)-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-thiazolyl)methyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-methoxy-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-ethoxy-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyloxy-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(N,N-dimethylamino)methyl-4-thiazolyl)-methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)-amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-pyrrolidinyl)methyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-propyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-methyl)propyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-methyl)propyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-ethyl)propyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-cyclopentyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-cyclohexyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1,1-dimethyl)ethyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-cyclobutyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-cyclopropyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-ethyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-ethenyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-propenyl)-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-cyclopentenyl)-4-thiazolyl)-methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)-methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-cyclohexenyl)-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((4-cyclopentenyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((4-cyclohexenyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(3-propenyl)-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-propenyl)-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-methyl-1-propenyl)-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-methyl-1-propenyl)-4-thiazolyl)-methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)-amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1,2-dimethyl-1-propenyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)-methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(cyclopentyl)methyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(cyclohexyl)methyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-phenyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-benzyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-phenyl)ethyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-phenyl-1-ethenyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)-methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(4-fluoro)phenyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-chloro)phenyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(3-methoxy)phenyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-thiazolyl)-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-thiazolyl)methyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-methoxy-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-ethoxy-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyloxy-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(N,N-dimethylamino)methyl-4-thiazolyl)-methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)-amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-pyrrolidinyl)methyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-propyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-methyl)propyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-methyl)propyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-ethyl)propyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-cyclopentyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-cyclohexyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1,1-dimethyl)ethyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-cyclobutyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-cyclopropyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-ethyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-ethenyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-propenyl)-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-cyclopentenyl)-4-thiazolyl)-methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)-methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-cyclohexenyl)-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((4-cyclopentenyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((4-cyclohexenyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(3-propenyl)-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-propenyl)-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-methyl-1-propenyl)-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-methyl-1-propenyl)-4-thiazolyl)-methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)-amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1,2-dimethyl-1-propenyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)-methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(cyclopentyl)methyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(cyclohexyl)methyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-phenyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-benzyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-phenyl)ethyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-phenyl-1-ethenyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)-methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(4-fluoro)phenyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-chloro)phenyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(3-methoxy)phenyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-thiazolyl)-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-thiazolyl)methyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-methoxy-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-ethoxy-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyloxy-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(N,N-dimethylamino)methyl-4-thiazolyl)-methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)-amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-pyrrolidinyl)methyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-propyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-methyl)propyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-methyl)propyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-ethyl)propyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)alaninyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Ethyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-2-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)valinyl)amino)-5-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)alaninyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((2-(N,N-Dimethylamino)-4-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-2-(N-(N-((2-(N,N-Dimethylamino)-4-thiazolyl)methoxycarbonyl)valinyl)amino)-5-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((2-(4-Morpholinyl)-4-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-2-(N-(N-((2-(4-Morpholinyl)-4-thiazolyl)-methoxycarbonyl)valinyl)amino)-5-(N-((5-oxazolyl)-methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((2-(1-Pyrrolidinyl)-4-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-2-(N-(N-((2-(1-Pyrrolidinyl)-4-thiazolyl)-methoxycarbonyl)valinyl)amino)-5-(N-((5-oxazolyl)-methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((3-Isopropyl-5-isoxazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)alaninyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Ethyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-2-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)valinyl)amino)-5-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)alaninyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((2-(N,N-Dimethylamino)-4-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-2-(N-(N-((2-(N,N-Dimethylamino)-4-thiazolyl)methoxycarbonyl)valinyl)amino)-5-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((2-(4-Morpholinyl)-4-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-2-(N-(N-((2-(4-Morpholinyl)-4-thiazolyl)-methoxycarbonyl)valinyl)amino)-5-(N-((5-isoxazolyl)-methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((2-(1-Pyrrolidinyl)-4-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-2-(N-(N-((2-(1-Pyrrolidinyl)-4-thiazolyl)-methoxycarbonyl)valinyl)amino)-5-(N-((5-isoxazolyl)-methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((3-Isopropyl-5-isoxazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)alaninyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Ethyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-2-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)valinyl)amino)-5-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)alaninyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((2-(N,N-Dimethylamino)-4-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-2-(N-(N-((2-(N,N-Dimethylamino)-4-thiazolyl)methoxycarbonyl)valinyl)amino)-5-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((2-(4-Morpholinyl)-4-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-2-(N-(N-((2-(4-Morpholinyl)-4-thiazolyl)-methoxycarbonyl)valinyl)amino)-5-(N-((5-isothiazolyl)-methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((2-(1-Pyrrolidinyl)-4-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-2-(N-(N-((2-(1-Pyrrolidinyl)-4-thiazolyl)-methoxycarbonyl)valinyl)amino)-5-(N-((5-isothiazolyl)-methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((3-Isopropyl-5-isoxazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Example 41

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-ethyl-4-oxazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedures of Example 18A - F, but replacing isobutyramide with propionamide, provided the desired compound. ^{1}H NMR (DMSO-d_6) δ 0.74 (d, J=6 Hz, 6H), 1.19 (t, J=7 Hz, 3H), 1.38-1.51 (m, 2H), 1.80-1.94 (m, 1H), 2.54-2.74 (m, 5H), 2.83 (s, 3H), 3.53-3.63 (m, 1H), 3.82 (br q, 1 H), 3.92 (t, J = 8 Hz, 1H), 4.13, (m, 1H), 4.26 (AA', 2 H), 4.63 (d, J=6 Hz, 1H), 5.13 (AA', 2H), 5.90 (d, J=9 Hz, 1H), 6.89 (d, J=9 Hz, 1H), 7.07-7.25 (m, 12H), 7.68 (d, J=8.7 Hz, 1H), 7.77 (s, 1H), 7.86 (s, 1H), 9.05 (s, 1H). Mass spectrum: $(M + H)^+ = 691$. Anal. Calcd for $C_{36}H_{46}N_6O_6S \cdot 0.3H_2O$: C, 62.10; H, 6.75; N, 12.07. Found: C, 62.42; H, 6.68; N, 11.69.

Example 42

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-methyl-4-oxazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedures of Example 18A - F, but replacing isobutyramide with acetamide, provided the desired compound. Mass spectrum: $(M + H)^+ = 677$.

Example 43

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-1-phenyl-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-6-(5-oxazolyl)-3-hydroxyhexane.

Using the procedures of Example 8C - 8K, but replacing 5-chloromethylthiazole hydrochloride with 5-chloromethyloxazole hydrochloride provided the desired compound.

Fluorogenic Assay for Screening Inhibitors of HIV Protease

The inhibitory potency of the compounds of the invention can be determined by the following method.

A compound of the invention is dissolved in DMSO and a small aliquot further diluted with DMSO to 100 times the final concentration desired for testing. The reaction is carried out in a 6 X 50 mm tube in a total volume of 300 microliters. The final concentrations of the components in the reaction buffer are: 125 mM sodium acetate, 1 M sodium chloride, 5 mM dithiothreitol, 0.5 mg/ml bovine serum albumin, 1.3 μM fluorogenic substrate, 2% (v/v) dimethylsulfoxide, pH 4.5. After addition of inhibitor, the reaction mixture is placed in the fluorometer cell holder and incubated at 30°C for several minutes. The reaction is initiated by the addition of a small aliquot of cold HIV protease. The fluorescence intensity (excitation 340 nM, emmision 490 nM) is recorded as a function of time. The reaction rate is determined for the first six to eight minutes. The observed rate is directly proportional to the moles of substrate cleaved per unit time. The percent inhibition is 100 X (1 - (rate in presence of inhibitor)/(rate in absence of inhibitor)).

Fluorogenic substrate: Dabcyl-Ser-Gln-Asn-Tyr-Pro-Ile-Val-Gln-EDANS wherein DABCYL = 4-(4-dimethylamino-phenyl)azobenzoic acid and EDANS = 5-((2-aminoethyl)amino)-naphthalene-1-sulfonic acid.

Table 1 shows the inhibitory potencies of compounds of the invention against HIV-1 protease.

TABLE 1

Compound of Example	Percent Inhibition	Inhibitor Concentration (nanomolar)
1	79	0.5
3	70	0.5
4	72	0.5
5	79	0.5
6	75	0.5
7	74	0.5
9	64	0.5
10	56	0.5
11	71	0.5
12	72	0.5
13	46	0.5
14	61	0.5
15	57	0.5
17	66	0.5
18	80	0.5
19	70	0.5
20	86	0.5
26	71	0.5
27	82	0.5
28	68	0.5
39	63	0.5
41	75	0.5
42	70	0.5

Antiviral Activity

The anti-HIV activity of the compounds of the invention can be determined in MT4 cells according to the procedure of Kempf, et. al. (*Antimicrob. Agents Chemother.* **1991**, *35*, 2209). The IC_{50} is the concentration of compound that gives 50% inhibition of the cytopathic effect of HIV. The LC_{50} is the concentration of compound at which 50% of the cells remain viable.

Table 2 shows the inhibitory potencies of compounds of the invention against HIV-1_{3B} in MT4 cells.

TABLE 2

Compound of Example	IC_{50} (micromolar)	LC_{50} (micromolar)
1	0.025-0.040	55
3	0.041-0.075	52
4	0.17-0.32	29
5	0.003-0.009	51
6	0.006-0.014	100
7	0.076-0.131	56
8	0.057-0.095	97
9	0.080-0.10	62
10	0.054-0.071	55
11	0.017-0.132	60
12	0.053-0.106	>100
13	0.056-0.088	56
14	0.14-0.22	>100
15	0..43-0.67	41

17	0.23-0.31	19
18	0.039-0.046	62
19	0.022-0.048	87
20	0.011-0.014	55
26	0.007-0.011	28
27	0.011-0.012	57
28	0.11-0.12	18
39	0.073-0.077	22
41	0.015-0.02	100
42	0.073-0.08	>100

The compounds of the present invention can be used in the form of salts derived from inorganic or organic acids. These salts include but are not limited to the following: acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, cyclopentanepropionate, dodecylsulfate, ethanesulfonate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxy-ethanesulfonate (isethionate), lactate, maleate, methanesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, p-toluenesulfonate and undecanoate. Also, the basic nitrogen-containing groups can be quaternized with such agents as loweralkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides, and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl, and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides, and others. Water or oil-soluble or dispersible products are thereby obtained.

Examples of acids which may be employed to form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, sulphuric acid and phosphoric acid and such organic acids as oxalic acid,

maleic acid, succinic acid and citric acid. Other salts include salts with alkali metals or alkaline earth metals, such as sodium, potassium, calcium or magnesium or with organic bases.

Preferred salts of the compounds of the invention include hydrochloride, methanesulfonate, sulfonate, phosphonate and isethionate.

The compounds of the present invention can also be used in the form of esters. Examples of such esters include a hydroxyl-substituted compound of formula **A** or **A1** which has been acylated with a blocked or unblocked amino acid residue, a phosphate function, a hemisuccinate residue, an acyl residue of the formula R*C(O)- or R*C(S)- wherein R* is hydrogen, loweralkyl, haloalkyl, alkoxy, thioalkoxy, alkoxyalkyl, thioalkoxyalkyl or haloalkoxy, or an acyl residue of the formula R_a-C(R_b)(R_d)-C(O)- or R_a-C(R_b)(R_d)-C(S)- wherein R_b and R_d are independently selected from hydrogen or loweralkyl and R_a is -N(R_e)(R_f), OR_e or -SR_e wherein R_e and R_f are independently selected from hydrogen, loweralkyl and haloalkyl, or an amino-acyl residue of the formula $R_{180}NH(CH_2)_2NHCH_2C(O)$- or $R_{180}NH(CH_2)_2OCH_2C(O)$- wherein R_{180} is hydrogen, loweralkyl, arylalkyl, cycloalkylalkyl, alkanoyl, benzoyl or an a-amino acyl group. The amino acid esters of particular interest are glycine and lysine; however, other amino acid residues can also be used, including those wherein the amino acyl group is -$C(O)CH_2NR_{200}R_{201}$ wherein R_{200} and R_{201} are independently selected from hydrogen and loweralkyl or the group -$NR_{200}R_{201}$ forms a nitrogen containing heterocyclic ring. These esters serve as pro-drugs of the compounds of the present invention and serve to increase the solubility of these substances in the gastrointestinal tract. These esters also serve to increase solubility for intravenous administration of the compounds. Other prodrugs include a hydroxyl-substituted compound of formula **A** or **A1** wherein the hydroxyl group is functionalized with a substituent of the formula -$CH(R_g)OC(O)R_{181}$ or -$CH(R_g)OC(S)R_{181}$ wherein R_{181} is loweralkyl, haloalkyl, alkoxy, thioalkoxy or haloalkoxy and R_g is hydrogen, loweralkyl, haloalkyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl or dialkylaminocarbonyl. Such prodrugs can be prepared according to the

procedure of Schreiber (Tetrahedron Lett. **1983**, *24*, 2363) by ozonolysis of the corresponding methallyl ether in methanol followed by treatment with acetic anhydride.

The prodrugs of this invention are metabolized in vivo to provide the hydroxyl-substituted compound of formula **A** or **A1**. The preparation of the prodrug esters is carried out by reacting a hydroxyl-substituted compound of formula **A** or **A1** with an activated amino acyl, phosphoryl, hemisuccinyl or acyl derivative as defined above. The resulting product is then deprotected to provide the desired pro-drug ester. Prodrugs of the invention can also be prepared by alkylation of the hydroxyl group with (haloalkyl)esters, transacetalization with bis-(alkanoyl)acetals or condensation of the hydroxyl group with an activated aldehyde followed by acylation of the intermediate hemiacetal.

The compounds of the invention are useful for inhibiting retroviral protease, in particular HIV protease, in vitro or in vivo (especially in mammals and in particular in humans). The compounds of the present invention are also useful for the inhibition of retroviruses in vivo, especially human immunodeficiency virus (HIV). The compounds of the present invention are also useful for the treatment or prophylaxis of diseases caused by retroviruses, especially acquired immune deficiency syndrome or an HIV infection in a human or other mammal.

Total daily dose administered to a human or other mammal host in single or divided doses may be in amounts, for example, from 0.001 to 300 mg/kg body weight daily and more usually 0.1 to 10 mg. Dosage unit compositions may contain such amounts of submultiples thereof to make up the daily dose.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex,

diet, time of administration, route of administration, rate of excretion, drug combination, and the severity of the particular disease undergoing therapy.

The compounds of the present invention may be administered orally, parenterally, sublingually, by inhalation spray, rectally, or topically in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles as desired. Topical administration may also involve the use of transdermal administration such as transdermal patches or iontophoresis devices. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection, or infusion techniques.

Injectable preparations, for example, sterile injectable aqueous or oleagenous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-propanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Suppositories for rectal administration of the drug can be prepared by mixing the drug with a suitable nonirritating excipient such as cocoa butter and polyethylene glycols which are solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum and release the drug.

Solid dosage forms for oral administration may include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound may be admixed with at least one inert diluent such as sucrose lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets, and pills, the dosage

forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

Liquid dosage forms for oral administration may include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

The compounds of the present invention can also be administered in the form of liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multi-lamellar hydrated liquid crystals that are dispersed in an aqueous medium. Any non-toxic, physiologically aceptable and metabolizable lipid capabale of forming liposomes can be used. The present compositions in liposome form can contain, in addition to a compound of the present invention, stabilizers, preservatives, excipients, and the like. The preferred lipids are the phospholipids and phosphatidyl cholines (lecithins), both natureal and synthetic.

Methods to form liposomes are known in the art. See, for example, Prescott, Ed., Methods in Cell Biology, Volume XIV, Academic Press, New York, N.Y. (1976), p. 33 et seq.

While the compounds of the invention can be administered as the sole active pharmaceutical agent, they can also be used in combination with one or more immunomodulators, antiviral agents, other antiinfective agents or vaccines. Other antiviral agents to be administered in combination with a compound of the present invention include AL-721, beta interferon, polymannoacetate, reverse transcriptase inhibitors (for example, dideoxycytidine (DDC), dideoxyinosine (DDI), BCH-189, AzdU, carbovir, DDA, D4C, D4T, DP-AZT, FLT (fluorothymidine), BCH-189, 5-halo-3'-thia-dideoxycytidine, PMEA, zidovudine (AZT) and the like), non-nucleoside reverse transcriptase inhibitors (for example, R82193, L-697,661, BI-RG-587

(nevirapine), retroviral protease inhibitors (for example, HIV protease inhibitors such as Ro 31-8959, SC-52151, KNI-227, KNI-272 and the like), HEPT compounds, L,697,639, R82150, U-87201E and the like), TAT inhibitors (for example, RO-24-7429 and the like), trisodium phosphonoformate, HPA-23, eflonithine, Peptide T, Reticulose (nucleophosphoprotein), ansamycin LM 427, trimetrexate, UA001, ribavirin, alpha interferon, oxetanocin, oxetanocin-G, cylobut-G, cyclobut-A, ara-M, BW882C87, foscarnet, BW256U87, BW348U87, L-693,989, BV ara-U, CMV triclonal antibodies, FIAC, HOE-602, HPMPC, MSL-109, TI-23, trifluridine, vidarabine, famciclovir, penciclovir, acyclovir, ganciclovir, castanospermine, rCD4/CD4-IgG, CD4-PE40, butyl-DNJ, hypericin, oxamyristic acid, dextran sulfate and pentosan polysulfate. Immunomodulators that can be administered in combination with a compound of the present invention include bropirimine, Ampligen, anti-human alpha interferon antibody, colony stimulting factor, CL246,738, Imreg-1, Imreg-2, diethydithiocarbamate, interleukin-2, alpha-interferon, inosine pranobex, methionine enkephalin, muramyl-tripeptide, TP-5, erythropoietin, naltrexone, tumor necrosis facator, beta interferon, gamma interferon, interleukin-3, interleukin-4, autologous CD8+ infusion, alpha interferon immunoglobulin, IGF-1, anti-Leu-3A, autovaccination, biostimulation, extracorporeal photophoresis, FK-565, FK-506, G-CSF, GM-CSF, hyperthermia, isopinosine, IVIG, HIVIG, passive immunotherapy and polio vaccine hyperimmunization. Other antiinfective agents that can be administered in combination with a compound of the present invention include pentamidine isethionate. Any of a variety of HIV or AIDS vaccines (for example, gp120 (recombinant), Env 2-3 (gp120), HIVAC-1e (gp120), gp160 (recombinant), VaxSyn HIV-1 (gp160), Immuno-Ag (gp160), HGP-30, HIV-Immunogen, p24 (recombinant), VaxSyn HIV-1 (p24) can be used in combination with a compound of the present invention.

Other agents that can be used in combination with the compounds of this invention are ansamycin LM 427, apurinic acid, ABPP, AI-721, carrisyn, AS-101, avarol, azimexon, colchicine, compound Q, CS-85, N-acetyl cysteine, (2-oxothiazolidine-4-carboxylate), D-penicillamine, diphenylhydantoin, EL-10,

erythropoieten, fusidic acid, glucan, HPA-23, human growth hormone, hydroxchloroquine, iscador, L-ofloxacin or other quinolone antibiotics, lentinan, lithium carbonate, MM-1, monolaurin, MTP-PE, naltrexone, neurotropin, ozone, PAI, panax ginseng, pentofylline, pentoxifylline, Peptide T, pine cone extract, polymannoacetate, reticulose, retrogen, ribavirin, ribozymes, RS-47, Sdc-28, silicotungstate, THA, thymic humoral factor, thymopentin, thymosin fraction 5, thymosin alpha one, thymostimulin, UA001, uridine, vitamin B12 and wobemugos.

Other agents that can be used in combination with the compounds of this invention are antifungals such as amphotericin B, clotrimazole, flucytosine, fluconazole, itraconazole, ketoconazole and nystatin and the like.

Other agents that can be used in combination with the compounds of this invention are antibacterials such as amikacin sulfate, azithromycin, ciprofloxacin, tosufloxacin, clarithromycin, clofazimine, ethambutol, isoniazid, pyrazinamide, rifabutin, rifampin, streptomycin and TLC G-65 and the like.

Other agents that can be used in combination with the compounds of this invention are anti-neoplastics such as alpha interferon, COMP (cyclophosphamide, vincristine, methotrexate and prednisone), etoposide, mBACOD (methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine and dexamethasone), PRO-MACE/MOPP(prednisone, methotrexate (w/leucovin rescue), doxorubicin, cyclophosphamide, etoposide/mechlorethamine, vincristine, prednisone and procarbazine), vincristine, vinblastine, angioinhibins, pentosan polysulfate, platelet factor 4 and SP-PG and the like.

Other agents that can be used in combination with the compounds of this invention are drugs for treating neurological disease such as peptide T, ritalin, lithium, elavil, phenytoin, carbamazipine, mexitetine, heparin and cytosine arabinoside and the like.

Other agents that can be used in combination with the compounds of this invention are anti-protozoals such as albendazole, azithromycin, clarithromycin, clindamycin, corticosteroids, dapsone, DIMP, eflornithine,

566C80, fansidar, furazolidone, L,671,329, letrazuril, metronidazole, paromycin, pefloxacin, pentamidine, piritrexim, primaquine, pyrimethamine, somatostatin, spiramycin, sulfadiazine, trimethoprim, TMP/SMX, trimetrexate and WR 6026 and the like.

Among the preferred agents for treatment of HIV or AIDS in combination with the compounds of this invention are reverse transcriptase inhibitors.

It will be understood that agents which can be combined with the compounds of the present invention for the treatment or prophylaxis of AIDS or an HIV infection are not limited to those listed above, but include in principle any agents useful for the treatment or prophylaxis of AIDS or an HIV infection.

When administered as a combination, the therapeutic agents can be formulated as separate compositions which are given at the same time or different times, or the therapeutic agents can be given as a single composition.

The foregoing is merely illustrative of the invention and is not intended to limit the invention to the disclosed compounds. Variations and changes which are obvious to one skilled in the art are intended to be within the scope and nature of the invention which are defined in the appended claims.